Parameters	UH-AC 62 XX Formulations		
	ZB 334	ZB 335	TK 736A
$T_{1/2}$ (hr)	8.0	8.33	5.0
$AUC_{0-\infty}$ (μg•hr/ml)	6.961	7.175	5.006
$MRT_{0-\infty}$ (hr)	10.71	12.84	6.65
C_{max} (μg/ml)	0.696	0.728	0.82

3.1.1.9. U80-0051 The elimination kinetics of radio-activity following oral administration of [^{14}C]UH-AC 62 XX by gelatin capsule to baboons. (Vol. 2.050, p 186)

Study Nº: 113650
Report Nº: U80-0051
Study Aims: To determine the elimination of UH-AC 62 XX following oral administration of [^{14}C]UH-AC 62 XX to baboons.
Compound: [redacted]
Dose and Route: [redacted]
Animals: 3 ♂ baboons
Study Date: Not stated.

Results: Mean PK parameters for each formulation are shown in the following table. Approximately 87% of radioactive dose were recovered in 4 days. Mean cumulative (0-96 hr) urinary and fecal excretions were 35% and 42% of radioactive dose, respectively.

Parameters	Mean	CV (%)
C_{max} (μg eq/ml)	34.15	29.6
T_{max} (hr)	6.0	33.3
$AUC_{0-\infty}$ (μg eq•hr/ml)	475.6	26.7
$MRT_{0-\infty}$ (hr)	11.2	18.7
$T_{1/2}$ (hr)	6.12	13.7
Clp (ml/min•kg)	0.022	31.3

3.1.2. REPEATED DOSE STUDIES OF THE PHARMACOKINETICS OF UH-AC 62 XX

3.1.2.1. U92-0449 Tissue distribution, whole body autoradiography and excretion balance after multiple oral administration of [^{14}C]UH-AC 62 XX to black hooded rats. (Vol. 2.050, p 208)

Study Nº: B 96
Report Nº: U92-0449
Study Aims: To determine tissue distribution and excretion balance of UH-AC 62 XX following oral administration with 1 mg/kg [^{14}C]UH-AC 62 XX to black hooded rats for 5 days.
Compound: [redacted]
Dose and Route: [redacted]
Dosing duration: 5-day
Animals: ♂ & ♀ black hooded rats [redacted] 9-14 weeks of age, weighing 192-230 g.
Study Date: Not stated.
Sample Collection: Urine and Feces - 0-8, 8-24, 24-48 hr.
Blood - 0.5, 1, 2, 3, 5, 8, 24, 48, 72, 96 hr post last dose.
Organs/Tissues - 5, 24, 48, and 72 hr post last dose.

Results:

- PK Parameters in Blood - Mean (±SD) PK parameters for [^{14}C]UH-AC 62 XX following 5-day repeated oral dosing are shown in the following table.

PK Parameters	♂	♀
AUC_{0-t} (μg eq•hr/ml)	12.34 ± 2.19	18.78 ± 2.07
C_{max} (μg eq/ml)	1.38 ± 0.16	1.49 ± 0.16
T_{max} (hr)	0.5	1

- Tissue Distribution - Results from quantitation of radioactivity in various tissues/organs showed that the liver and kidney had highest concentrations of radioactivity. Blood and thyroid gland also showed significant amounts of exposure. Lower levels were seen in the lungs, trachea, heart, skin, pancreas, and salivary glands. The brain and eyes had very low but detectable amounts of radioactivity.
- Metabolic Pattern in Urine - Radiochromatograms showed that both ♂ and ♀ black hooded rats had identical peaks in the metabolic pattern. Similar pattern was observed for albino rats indicating that both strains of rats had the same metabolic pathways for [^{14}C]UH-AC 62 XX.
- Urine and Fecal Excretion - Aprroximately 68-75% of radioactive dose was eliminated through renal excretion at 48 hr post last dosing in pigmented rats. Mean (n=3) cumulative urine and fecal excretions expressed as % radioactive dose for ♂ and ♀ rats after receiving 5-repeated oral doses are listed in the following table. It appered that ♀ rats had slower urinay elimination rate.

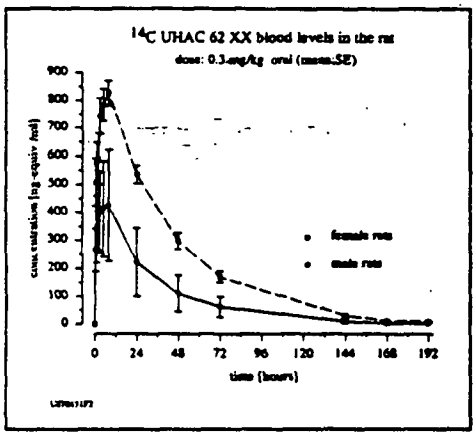
Time (hr)	Black Hooded Rats						Albino Rats					
	♂			♀			♂			♀		
	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
0-8	51.0	-	-	27.0	-	-	19.2	-	-	6.2	-	
0-24	72.2	15.5	87.7	58.4	13.1	71.6	48.2	15.6	65.7	22.1	8.2	30.3
0-48	75.0	18.0	93.0	68.3	19.9	88.2	60.5	24.7	85.3	35.9	19.2	55.1
0-72	-	-	-	-	-	-	63.8	27.2	91.0	43.6	25.7	69.3

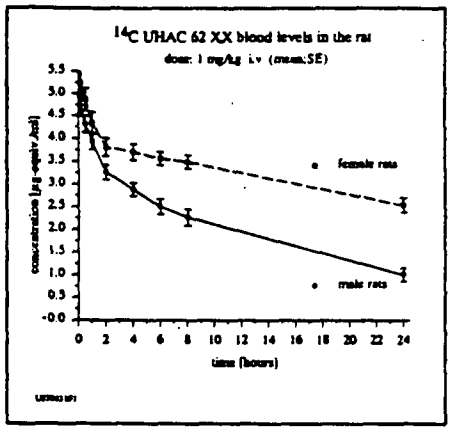
3.1.2.2. U93-0299 Sex-specific differences in the pharmacokinetics of UH-AC 62 XX, a new non-steroidal anti-inflammatory drug (NSAID), in rats. (Vol. 2.050, p 269)

Study Nº: B117
Report Nº: U93-0299
Study Aims: To determine sex differences in the PK of UH-AC 62 XX following single or multiple (11-doses) oral or iv administration in rats.
Compound: [redacted]
Dose and Route: [redacted]
Dosing Frequency: Single dose or 11-dose
Animals: ♂ & ♀ rats, [redacted] SPF), weighing 200-220 g.
Study Date: Not stated.
Blood Collection: 10 and 30 min, 1, 2, 4, 6, 8, 24, 48, 72, 144, 168 and 192 hr post-dose.
Urine Sampling: 0-8, and 8-24 hr post doing.

Results:

- Blood Levels - Higher plasma levels of radioactivity as depicted in the following two figures with higher AUC values were detected in ♀ rats following a single dose of [^{14}C]UH-AC 62 XX at 0.3 mg/kg by gavage or 1 mg/kg iv. The mean PK parameters for UH-AC 62 XX after repeated oral dosing (0.3 or 1.0 mg/kg/day po x 11) with [^{14}C]UH-AC 62 XX are summarized in the following table. Gender-related differences in plasma levels and exposure expressed as AUC were noted.





PK parameters	Dose (mg/kg)			
	1.0		0.3	
	♂	♀	♂	♀
C_{max} (µg eq/ml)	6.4	7.5	1.48	2.44
T_{max} (hr)	4.2	13.1	5.2	8.31
AUC (µg eq•hr/ml)	172	437	38.8	153
MRT_{iv} (hr)	24.0	48.6	20.7	55.8
$T_{½}$ (hr)	15.5	29.6	12.6	36.7

- Renal Excretion - Reduced (~50% less than that in ♂) urine excretion of radioactivity was observed in ♀ at 8 and 24 hr post dosing. Similar findings were observed in the studies with albino rats. Mean % radioactive dose excreted in the urine following a single oral dose of 1 mg/kg [^{14}C]UH-AC 62 XX is listed in the following table.

Time (hr)	% Dose Excreted in Urine	
	♂	♀
0-8	17.9	6.0
8-24	22.1	12.2
0-24	40.0	18.2

- Metabolic Patterns in Plasma and Urine - Metabolic patterns of UH-AC 62 XX in the plasma and urine were determined by a TLC method. Based on the presented TLC grams, it appeared that higher concentrations of radioactivity present in the plsama and urine of ♀ rats were from unchanged parent drug, UH-AC 62 XX.

3.1.2.3. P98-6381 Pharmacokinetics of meloxicam in animals and the relevance to humans. Drug Metabolism and Disposition, 1998, 26(6): 576-584. (Vol. 2.050, p 295)

The contents of this submitted publication were collected from various study reports that had been thoroughly reviewed; therefore, review of this manuscript was not performed.

3.2. DISTRIBUTION

3.2.1. SINGLE DOSE STUDIES OF THE DISTRIBUTION OF UH-AC 62 XX

3.2.1.1. U88-0182 Distribution of UH-AC 62 XX in plasma and milk of the rat. (Vol. 2.049, p 1)

Study Nº: ADME 2/88

Report Nº: U88-0182
Study Aims: To determine distribution of UH-AC 62 XX in plasma and milk following administration of [^{14}C]UH-AC 62 XX to nursing rats with 9-11 days old pups.
Compound:
Dose and Route:
Animals: Albino ♀ rats with 9-11 days old pups, weighing 310-370 g
Study Date: Not stated.
Metabolic Profile Determination:

Results:

- Drug Levels in Blood and Milk - The levels (μg eq/ml) of total radioactivity dose in the blood, plasma, and milk following a single oral dose of 5 mg/kg [^{14}C]UH-AC 62 XX are presented in the following table.

Time (hr)	Whole Blood	Plasma	C_{RBC}/C_{plasma}	Milk	C_{milk}/C_{plasma}
1	7.90	12.62	0.11	9.71	0.77
5	11.26	18.36	0.06	22.34	1.22
24	3.60	5.97	0.06	9.93	1.66

- Meatabolic Patterns in Blood and Milk - **The submitted figures with TLC migration diagrams wer obscure and uninterpretable.**

Therefore, [^{14}C]UH-AC 62 XX was excreted into milk extensively and available to neonates.

3.2.1.2. U87-0267 Tissue distribution and excretion balance of UH-AC 62 XX in pigmented rats. (Vol. 2.049, p 261)

Study Nº: ADME 24/88
Report Nº: 87-0267
Study Aims: To determine tissue distribution of [^{14}C]UH-AC 62 XX in pigmented rats following a single iv and oral administrations.
Compound:
Dose and Route:
Animals: ♂ rats, weighing 200 g
Study Date: Not stated.
Sampling: iv - 1, 9, 24, 48, and 96 hr and 12 and 16 days post does
oral - 5, 9, 24, 48, and 96 hr and 12 and 16 days post does.
Radioactivity Determination:

Results:

- Tissue Distribution of Radioactivity - The highest concentrations of radioactivity was found in the blood at 1 or 5 and 9 hr post iv and oral administration. Well perfused tissue/organs, such as lungs, heart, liver, and kidneys, also contained high levels of radioactivity. The following table lists distribution of the total radioactivity in rat tissues and excreta after a single iv and oral administration of 1 mg/kg [^{14}C]UH-AC 62 XX.

Tissue/Organs	Tissue Distribution of Radioactivity (%) following iv/oral Administration															
	1 h	5 h	9 h		24 h		48 h		96 h		8 d		12 d		16 d	
	iv	po	iv	po	iv	po	iv	po	iv	po	iv	po	iv	po	iv	po
Brain	0.09	0.09	0.07	0.06	(0.03)	0.04	-	-	-	-	-	-	-	-	-	-
Eyes	0.02	0.01	0.03	0.03	0.02	0.02	(0.01)	-	-	-	-	-	-	-	-	-
Lungs	0.81	0.68	0.28	0.21	0.13	0.15	0.06	(0.04)	-	(0.04)	-	-	-	-	-	-
Heart	0.74	1.44	0.25	0.21	0.08	0.10	(0.04)	(0.04)	-	-	-	-	-	-	-	-
Stomach + Contents	0. 34	0.83	0.27	0.64	0.17	(0.14)	0.06	(0.05)	(0.04)	-	-	-	-	-	-	-
Small Intestines + Contents	2.67	3.71	2.60	3.27	1.40	1.51	0.66	0.39	(0.17)	(0.17)	-	-	-	-	-	-
Large Intestines + Contests	0.94	2.05	2.72	2.7	4.82	2.89	1.77	1.92	0.67	0.42	(0.20)	(0.17)	(0.21)	(0.07)	(0.12)	(0.14)
Liver	10.94	10.24	7.12	10.05	3.68	6.41	2.10	0.86	0.54	0.89	0.22	0.22	0.25	(0.10)	(0.11)	(0.11)
Spleen	0.12	0.15	0.06	0.06	0.04	0.04	(0.02)	(0.02)	(0.02)	-	(0.02)	-	-	-	-	-
Kidneys	1.88	1.58	1.09	1.30	0.45	0.85	0.27	0.1.1	0.07	0.05	(0.03)	(0.04)	(0.03)	-	-	(0.03)
Adrenals	0.02	0.02	0.02	(0.02)	(0.01)	-	-	-		-		-		-		-
Testes	0.53	0.75	0.80	0.64	0.48	0.37	0.15	0.08	(0.05)	-	-	-	-	-	-	-
Fat (Peri-Intestinal)	3.19	1.90	2.39	2.64	1.04	0.92	0.39	(0.1.9	(0.14)	-	-		-	-	-	-
Fat (Skeletal Muscle)	1.17	4.27	3.21	3.74	1.61	1. 65	0.66	0.43	0.29	(020)	-	-	-	-	-	-
Skeletal Muscle	14.29	8.84	2.63	11.30	5.78	8.01	1.78	1.80	1.18	(0.62)	-	-	-	-	-	-
Skin (Non-Pigmented)	10.17	9.55	9.18	11.49	6.50	5.24	2.92	2.17	1.42	1.11	-	(0.92)	(0.05)	-	(1.00)	-
Skin (Pigmented)	4.07	5.60	4.81	3.96	2.45	2.57	0.47	0.71	0.95	0.50	-	(0.31)	(0.39)	(0.39)	(0.35)	-
Residual Carcass	16.90	14.62	11.90	12.46	6.20	7.27	2.63	2.28	(1.71)	-	-	-	-	-	-	-
Whole Blood	21.84	19.39	16.63	15.24	6.90	8.07	2.40	1.81	1.03	(0.60)	-	-	-	-	-	-
Urine	0.70	7.32	13.81	15.80	52.17	40.82	60.06	65.32	63.99	68.69	60.81	69.27	64.09	70.97	66.24	65. 02
Feces					4.32	9.45	20.95	18.98	24.85	23.66	31.50	25.81	25.97	28.47	28.20	26.44
Total Recovery (% Dose)	91.53	93.29	89.87	96.77	98.28	96.35	97.44	97.20	97.12	97.15	92. 78	96.75	91.79	100.0	96.02	91 74

- Excretion in Urine and Feces - Cumulative (0-16 days) % excretions of radioactive dose in the urine and feces were 66% and 28%, respectively, post single iv dose and 65% and 26%, respectively, following a sigle oral dose.

3.2.1.3. U95-0668 Placental transfer of [^{14}C]UH-AC 62 XX in rats. 27 November 1995. (Vol. 2.046, p 1)

Study Nº: NBIBC-9528
Report Nº: U95-0668
Study Aims: To assess placental transfer of radioactivity following oral administration of [^{14}C]UH-AC 62 XX to the pregnant rats on Gestation Days 13 or 18.
Compound:
Dose and Route:
Animal: Pregnant ♀ (SPF) rats, 12-13 weeks of age, weighing 277-315 g on Gestation Day 13 and 326-375 g on Gestation Day 18.
Study Site:
Study Date: 11/27/1995
GLP/QAC Compliance: Not Stated.
Study Design: Pregnant rats (N=6 for Gestation Day 13 rats and n=12 for Gestation Day 18 rats) were dosed with 1 mg/kg of [^{14}C]UH-AC 62 XX. Blood samples (3/time point) were taken at 1, 4, 48, and 168 (for Gestation Day 13 rats only) hr post dose. Two rats dosed at Gestation Day 18 were allowed to litter. Pups were sacrificed on Days 3 and 6 postpartum. Tissues samples as shown in the following table were obtained for radioactivity determination. Radioactivity in the tissue homogenates was measured in a liquid scintillation counter.

Tissue Samples Obtained on Gestation Day 13	Tissue Samples Obtained on Gestation Day 18	Tissue Samples Obtained from Pups on Days 3 and 6 Post partum
Liver	Fetal Liver	Liver
Lung	Fetal Kidney	Kidney
Kidney	Fetal Lung	Lung
Placenta	Fetal Heart	Heart
Fetus	Placenta	Stomach
Amniotic Fluid	Amniotic Fluid	Intestine

Results: It appeared that the rats dosed on Gestation Day 18 had higher levels of radioactivity in the fetus and amniotic fluid than the rats dosed on Gestation Day 13. Newborn rats retained radioactivity >6 days after delivery. Tissue radioactivity after oral administration of 1 mg/kg of [^{14}C]UH-AC 62 XX rats on Gestation Day 13 or 18 are presented in the following table.

Tissues	Concentration (ng eq./g or ml) (n)			
	1 hr	4 hr	48 hr	168 hr
Gestation Day 13				
Blood	1174.7 ± 69.6 (3)	2500.1 ± 776.6 (3)	1787.3 ± 347.2 (3)	351.3 ± 162.4(3)
Plasma	1877.4 ±109.3(3)	3569.7 ± 1193.2 (3)	2683.8 ± 509.1(3)	507.3 ± 229.7(3)
Liver	904.4 ± 294.5 (3)	2439.3 ± 367.3 (3)	1527.7 ± 310.6 (3)	398.2 ± 96.3 (3)
Kidney	485.9 ± 60.8 (3)	1253.0 ± 181.3 (3)	1176.0 ± 155.2 (3)	228.8 ± 55.3 (3)
Lung	454.6 ± 26.4 (3)	1011.2 ± 330.1 (3)	712.7 ± 95.8 (3)	152.3 ± 67.2 (3)
Heart	270.1 ± 3.9 (3)	600.4 ± 189.9 (3)	436.1 ± 73.6 (3)	97.7 ± 39.2 (3)
Placenta	229.0 ± 45.8 (6)	643.6 ± 242.8 (6)	376.3 ± 121.5 (6)	198.0 ± 78.6 (6)
Amniotic fluid	19.8 ±10.0 (6)	36.1 ± 4.3 (6)	112.4 ± 26.0 (6)	146.3 ± 75.8 (6)
Fetus	11.3 ± 3.7 (6)	37.4 ± 10.0 (6)	105.0 ± 15.3 (6)	149.7 ± 68.5 (6)
Gestation Day 18				
Blood	1142.8 ± 835.7 (3)	2029.4 ± 335.4 (3)	1587.2 ±29.6 (3)	
Plasma	1670.9 ± 1374.1 (3)	2748.3 (2)	2390.7 ± 461.6 (3)	
Liver	4558.9 ± 1184.2 (3)	2174.9 ±282.6 (3)	2198.1 ± 624.7 (3)	
Kidney	2194.8 ± 865.7 (3)	983.9 ± 59.4 (3)	809.2 ± 243.1 (3)	
Lung	689.6 (2)	792.7 ±54.7 (3)	743.9 ± 92.3 (3)	
Heart	610.4 ± 383.3 (3)	494.9 ± 89.4 (3)	367.8 ± 82.3 (3)	
Placenta	295.0 ± 136.6 (12)	548.8 ± 113.9 (12)	775.1 ± 234.1 (12)	
Amniotic fluid	36.0 ± 10.2 (12)	61.5 ± 12.5 (11)	734.7 ± 139.9 (12)	
Fetus	245.9 ± 105.1 (6)	213.9 ± 15.8 (6)	718.5 ± 249.3 (6)	
Fetal liver	202.4 ± 89.8 (6)	147.9 ± 24.8 (6)	362.3 ± 155.2 (6)	
Fetal kidney	226.4 ± 99.9 (6)	173.5 ±33.3 (6)	364.4 ± 1472 (6)	
Fetal lung	232.3 ± 112.7 (45)	149.9 ± 36.1 (6)	237.9 ± 105.9 (6)	
Fetal heart	227.8 ± 106.9 (6)	145.3 ± 36.3 (6)	292.4 ± 118.5 (6)	

Each value represents the mean ± S.D.

The following table shows tissue radioactivity concentrations in pups, maternal blood and plasma after oral administration of 1 mg/kg of [^{14}C]UH-AC 62 XX to pregnant rats on Gestation Day 18.

Tissues	Concentration (ng eq./g or ml) (n)	
	Lactation Day 3	Lactation Day 6
Dam		
Blood		89.5 (2)
Plasma		132.3 (2)
Pups		
Liver	821.0 ± 99.5 (4)	677.6 ± 168.7 (4)
Kidney	619.2 ± 178.1 (4)	407.3 ± 97.2 (4)
Lung	620.3 ± 200.1 (4)	407.2 ± 71.2 (4)
Heart	432.9 ± 109.0 (4)	312.2 ± 60.9 (4)
Stomach	522.8 ± 104.4 (4)	148.5 ± 48.6 (4)
Intestine	1085.5 ± 149.0 (4)	719.8 ± 356.2 (4)
Carcass	493.3 ± 192.7 (4)	301.0 ± 67.9 (4)
Total (Whole body)	541.8 ± 160.1 (4)	334.3 ± 85.7 (4)

Each value represents the mean S.D.

3.2.1.4. U91-0385 Tissue distribution, protein binding, excretion balance and metabolite pattern from plasma, urine and bile after oral administration in the male and female minipig. (Vol. 2.052, p 25)

Study Nº: 1512B
Report Nº: U91-0385
Study Aims: To determine tissue distribution of UH-AC 62 XX following a single oral dose.
Compound:
Dose and Route:
Animal: 1♂ + 1♀ minipigs, ~13 kg.
Study Date: Not Indicated
GLP/QAC Compliance: Not Stated.
Study Design: Pigs were given a single oral dose of [^{14}C]UH-AC 62 XX, 3.5 mg/kg, by gavage. The following samples were collected: urine, 0-4 hr; bile, 4 hr; and plasma, 4 h for metabolic pattern determination. Animals were sacrificed at 4 hr post dosing and tissues/organs were recovered for the radioactivity determination.

Results:

- Tissue distribution of Radioactivity - Tissue distribution of radioactivity in ♂ and ♀ pigs is listed in the following table. The total recovery of radioactivity was 82 and 71% in ♂ and ♀, respectively. The highest concentrations of radioactivity were identified in the intestines, kidneys, liver and bile.

Tissues	% Radioactive Dose		ng/g		Tissues	% Radioactive Dose		ng/g	
	♂	♀	♂	♀		♂	♀	♂	♀
Brain	0.04	0.02	227	108	Spleen	0.01	0.03	596	661
Hypophysis	0.00	0.00	703	565	Kidneys	1.38	0.57	8827	5446
Eyes	0.02	0.01	593	242	Adrenals	0.00	0.00	837	598
Submandibular Gland	0.03	0.02	910	633	Testis	0.06	-	535	-
Sublingual Gland	0.02	0.01	1193	807	Epididymis	0. 04	-	799	-
Parotid Gland	0.07	0.06	635	368	Muscle			411	324
Thyroid Gland	0.00	0.00	618	626	Skin			754	1744
Trachea			810	795	Bone			1336	634
Thymus			-	1042	Cartilage			2011	667
Lungs	0.17	0.00	764	1421	Urine	32.04	16.57		
Heart	0.19	0.32	1161	743	Bile	1.98	7.87		
Stomach	1.08	0.10	2548	38997	Stomach Content	0.31	13.05		
Small Intestine	12.16	14.80	14749	8119	Sm. Intest. Content	16.17	4.05		
Large Intestine	1.08	5.41	2554	3022	Feces	9.41	2.27		-
Liver	3.20	2.03	6680	8081	Plasma			2581	2842
Diaphragm		4.13	773	1294	Synovia			1328	1351
Pancreas	0.03	0.06	607	569	Total	81.55	71.38		

- Metabolic Pattern in Plasma, Urine and Bile - The major metabolites identified in the plasma, urine and bile were UH-AC 110 SE (acid) and AF-UH 1 (alcohol). At 4 hr post dosing, the majority of radioactivity present in the plasma was derived from unchanged parent drug. The following table shows metabolites as % radioactive dose in urine, bile and plasma following a single oral dose administration.

Sample	UH-AC 62 XX		UH-AC 110 SE		AF-UH 1		Not Retained	
	♂	♀	♂	♀	♂	♀	♂	♀
Plasma (4 hr)	81.9	93.4	2.1	-	4.6	2.8	14.3	8.8
Urine (0-4 hr)	2.9	-	8.9	10.4	54.3	45.7	-	-
Bile (4 hr)	2.6	1.0	56.0	97.0	34.0	2.0	2.3	-

- *In Vivo* Plasma Protein Binding - Approximately [redacted] of [^{14}C]-UH-AC 62 XX were protein bound.

3.2.2. *REPEATED DOSE STUDIES OF THE DISTRIBUTION OF UH-AC 62 XX*

3.2.2.1. U92-0467 Distribution of radioactive labeled UH-AC 62 XX in joints of rats with adjuvant arthritis. (Vol. 2.052, p 56)

Study Nº: B 100
Report Nº: U92-0467
Study Aims: To distribution of UH-AC 62 XX in joints following a single oral dose administration of [^{14}C]UH-AC 62 XX to *Mycobactericum butyricum* induced arthritis rats.
Compound: [redacted]
Dose and Route: [redacted]
Animal: ♂ [redacted] (SPF) rats, weighing 220-250 g, 4/group
Study Date: March 1985 - June 1986
GLP/QAC Compliance: Not Stated.
Study Design: Rats were given a single dose of 5 mg/kg [^{14}C]UH-AC 62 XX 21 days post induction of arthritis in the right hind foot-pad with *Mycobactericum butyricum*. Animals were sacrificed at 5, 8, and 24 hr post dosing and tissue sections from each leg were processed for autoradiography.

Results: High amounts of radioactivity were found to localize in the inflamed tissues and joint 5 - 24 hr post dosing.

3.3. METABOLISM

3.3.1. *SINGLE DOSE*

3.3.1.1. U87-0170 Isolation and structure elucidation of the main metabolites in the urine of rats after oral administration of [^{14}C]-UH-AC 62 XX. (Vol. 2.052, p 74)

Study Nº: ADME 42/86
Report Nº: U87-0170
Study Aims: To isolate and determine the structure of major metabolites in rat urine following a single oral dose of 10 mg/kg [^{14}C]UH-AC 62 XX.
Compound: [redacted]
Dose and Route: [redacted]
Animals: 8 ♂ rats, weighing ~250 g.
Study Date: Not Indicated
Urine Sampling: 0-8, 8-24, 2and 4-48 hr post doing.

UH-AC 62 XX Metabolic Pattern in Urine:

Results: The major metabolites identified in the rat urine as shown in the right figure were acid metabolite (UH-AC110; peak 5, 15.6%), alcohol metabolite (UH-AF1; peak 7, 31.4%), and DS-AC 2 SE, a metabolite with the cleavage of side chain, (peak 3, 21.7%).

3.3.1.2. U90-0659 Isolation and structure elucidation of the most polar metabolite of UH-AC 62 XX in man. (Vol. 2.052, p 102)

Not Reviewed.

3.3.1.3. U97-2622 Investigations of the metabolism of meloxicam in rats, presence of BIBO 8032 NA in rat urine. (Vol. 2.052, p 126)

Study Nº: B 806
Report Nº: U97-2622
Study Aims: To determine whether a highly polar metabolite, BIBO 8.32 NA, present in the rat urine following a single oral dose of 10 mg/kg [^{14}C]UH-AC 62 XX.
Compound:
Dose and Route:
Animals: ♂ & ♀ Wistar rats, (SPF), weighing 221-241 g, 3/sex/group.
Study Date: Not Indicated
Urine Sampling: 0-24 hr post doing.
UH-AC 62 XX Metabolic Pattern in Urine:

Results:

- Excretion in Urine- Mean % dose excretion in 0-24 hr urine is shown in the below table. BIBO 8.32 NA represented ~4.7% of total metabolite excreted in the urine of ♂ rats that received a dose of 10 mg/kg of UH-AC 62 XX.

Dose	% Dose Excreted in Urine	
(mg/kg)	♂	♀
1	52.5	15.2
10	48.9	13.8

Note: **The results shown in the table (Vol. 2.052, p 136) submitted by the sponsor were not clearly presented. Mean % of dose ± "SE or SD" was not indicated reflecting the inadequate quality of the submission.**

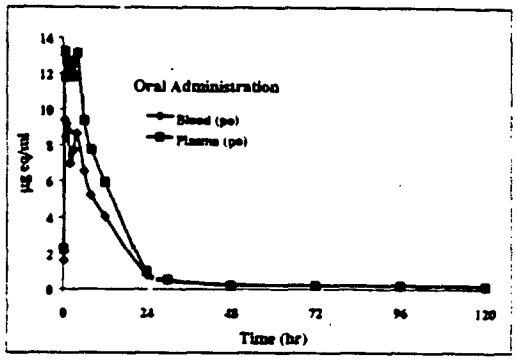
3.3.1.4. U82-0076 The metabolism and pharmacokinetics of [^{14}C]-UH-AC 62 XX in the minipig following oral and intravenous administration. (Vol. 2.050, p 125)

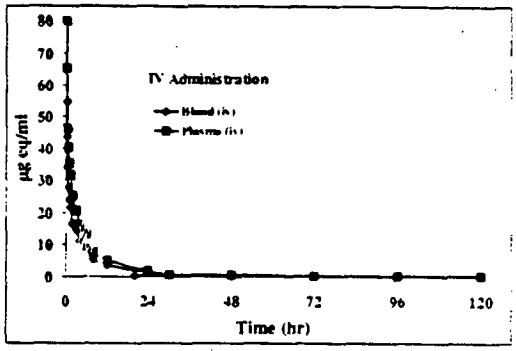
Study Nº: IRI 116845
Report Nº: U82-0076
Study Aims: To determine the rate and routes of elimination of radioactivity and the profiles of radioactivity in the blood and plasma of ♂ minipigs following a single oral or iv dose of 10 mg/kg [^{14}C]UH-AC 62 XX.
Compound:
Dose and Route:
Animals: 4♂ minipigs, weighing 13-18 kg.
Study Date: 1/19/1981 - 7/15/1981
Study Site:

Blood Collection: po - 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 48, 72, 96, and 120 h post dose
iv - 2, 7, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 48, 72, 96, 120 h post dose

Urine Sampling: po - 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, and 96-120 h post dose
iv - 0-6, 6-24, 24-48, 48-72, 72-96, and 96-120 h post dose

Fecal Sampling: po and iv - 24 hr intervals up to 120 hr post dose





Results:

- PK in Blood and Plasma - The total radioactivity in the plasma and whole blood after oral and iv administration of 10 mg/kg [^{14}C]UH-AC 62 XX is depicted in the right two figures. Mean plasma PK parameters for UH-AC 62 XX is presented in the following table.

Parameters	po		iv	
	Mean	CV (%)	Mean	CV (%)
C_{max} (µg eq/ml)	15.35	21.8	-	-
T_{max} (hr)	3.0	57.7	-	-
$AUC_{0-\infty}$ (µg eq•hr/ml)	214	14.5	24.3	24.9
$MRT_{0-\infty}$ (hr)	67.5	27.5	67.4	34.1
$T_{1/2}$ (hr)	145	23.0	121	12.0
Clp (l/hr•kg)	0.047	15.5	0.043	22.0

- Excretion in Urine and Feces - The total radioactivity recovered 120 hr post oral and iv dosing was ~86%. Cumulative total radioactivity (0-120 hr) eliminated through the feces was lightly higher than that in the urine. Cumulative excretion of radioactivity, expressed as % dose, in the urine and feces at various time points after iv and oral dosing is shown in the following table.

Time (hr)	Urine	Feces	Cage Wash	Cage Debris	Total	Urine	Feces	Cage Wash	Cage Debris	Total
	Oral					IV				
0 - 6	6.6					23.4				
0 - 12	16.6									
0 - 24	30.5	16.5	4.7	0.5	52.2	36.7	1.1	1.2	0.1	39.0
0 - 48	32.9	39.1	5.2	0.8	78.0	38.0	23.6	2.3	0.1	64.0
0 - 72	33.2	44.4		1.0	83.9	38.4	38.5		0.1	79.3
0 - 96	33.4	45.5		1.1	85.2	38.6	42.9		0.2	84.0
0 - 120	33.5	45.8	5.6	1.3	86.4	38.9	43.6	3.4	0.2	86.0

- Metabolic Profile in Plasma, Urine, and Feces - The major radioactivity (~60-80%) detected in the plasma was derived from unchanged drug following both oral and iv dosing. The unchanged drug represented ~1% and 17% in the urine and feces, respectively, after both oral and iv administrations. Two major metablites, M1 and M2, were detected in the urine and feces. M1 might be a conjugate of M2. About 50% and 5-6% of radioactivity in the feces derived from M2 and M1, respectively. In contrast, M1 and M2 comprised ~34 and 13% of radioactivity, respectively in the urine.

3.3.2. REPEATED DOSE

3.3.2.1. U92-0243 Effect of UH-AC 62 XX on cytochrome P 450 dependent monooxygenase in rats. (Vol. 2.052, p 159)

Study Nº: B77
Report Nº: U92-0243
Study Aims: To determine the effect of UH-AC 62 XX on cytochrome P-450 dependent mono-oxygenase in rats following oral administration of 15 mg/kg for 3 days.
Compound:
Dose and Route:
Animals: ♂ albino rats, weighing 200-250 g, 4/group.
Study Date: Not stated.
Study Design: Groups of 4 ♂ rats were dosed with either vehicle or 15 mg/kg of UH-AC 62 XX for 3 days. Animals were sacrificed at the end of study and livers were removed for the preparation of microsomes.

Results: Data showed that treatment of rats with UH-AC 62 XX, 15 mg/kg po, for 3 days did not alter the relative liver weight, protein and P-450 content, and metabolic enzyme activities (EROD, PROD, and ECOD).

Note: In the material and method section did not state that radio-labeled compound was employed for the study; however, the structure of UH-AC 62 XX depicted in p. 161, Vol. 2.052 (Amendment 1) clearly indicating that it was a radioisotope labeled compound.

3.4. PROTEIN BINDING

3.4.1.1. U95-2153 Supplementary investigations on pharmacokinetics in mice - protein binding and metabolism. 18 August 1995. (Vol. 2.049, p 211)

Study Nº: B461
Report Nº: U95-2153
Study Aims: To determine (1) metabolic pattern in the plasma and urine (2) the extent of plasma-protein binding of [^{14}C]UH-AC 62 XX in the mouse following an oral administration of 10 mg/kg [^{14}C]UH-AC 62 XX.
Compound:
Dose and Route:
Animals: ♂ albino mice, weighing 20-25 g, 3/time point.
Study Date: 7/1993 - 4/1995
Blood Sampling: 0.5, 2, and 5 hr post-dose
Urine Sampling: 0-4, 4-8, 8-24, 24-32 and 32-48 h post doing.
Feces: 0-4, 4-24, and 24-48 hr.
Radioactivity Determination:
UH-AC 62 XX Metabolic Pattern in Plasma and Urine:
Protein Binding:

Results:
Absorption - [^{14}C]UH-AC 62 XX was absorbed and systemically available after oral administration of 10 mg/kg to mice; plasma levels of total radioactivity are presented in the following table.

Time (h)	N	Plasma Levels (μg eq/ml)
0.5	3	9.91
2	2	6.90
5	3	3.54

Elimination - The elimination of radioactivity was primarily through urinary (67%) and fecal (35%) excretions. Approximately 50% of total radioactivity dose was detected in the urine by 8 hr post dose as shown in the following table.

Time (hr)	Urine + Cage Wash	Feces	Total Excretion
0-4	33.0	No Sample	33.0
0-8	54.1	26.0	80.1
0-24	66.5	35.9	102.4
0-32	67.2	No Sample	103.1 (??)
0-48	67.9	37.2	105.1

Plasma and Urine Metabolic Profile - About 83-87% of radioactivity present in the plasma was as parent compound and ~6-7% of radioactivity was derived from AF-UH 1 (5'-hydroxymethyl metabolite). The major metabolites identified in the urine were 5'-hydroxymethyl metabolite (AF-UH 1) (51%), 5'-carboxyl metabolite (UH-AC 110) (4.5%), and thiourea derivative (UH-AC 101) (2.8%) as shown in the right figure.

Protein-Binding - Approximately 97% of the drug were protein bound over the range of 0.5-20.0 μg/ml of [^{14}C]UH-AC 62 XX.

Note: As shown in the above table (Vol. 2.049, p 234), no fecal sample was obtained during 0-32 hr; therefore, the total excretion of radioactivity was not determinable for this period of time. Yet, the report showed 103.1% of radioactivity was recovered. The sponsor needs to describe how this number (103.1) was derived.

3.4.1.2. U89-0191 Determination of the protein binding of [^{14}C]UH-AC 62 XX to human and rat plasma by ultracentrifugation. (Vol. 2.052, p 11)

Report Nº: U89-0191

Study Aims: To determine plasma-protein binding of [^{14}C]UH-AC 62 XX with rat (*in vitro* and *in vivo)* and human plasma (*in vitro* only) [redacted] 100,000 x g at 27°C for 16-17 hr).

Compound: [^{14}C]UH-AC 62 XX (Lot Nº: not specified)

Plasma Samples: ♂ albino rat [redacted] plasma and plasma from healthy human donors

Results:

- *In Vitro* - Results showed approximately 99% UH-AC 62 XX bound to human plasma proteins at concentrations of [redacted] and to rat plasma protein [redacted] UH-AC 62 XX at concentrations of [redacted]
- *In Vivo* - More than 99% of UH-AC 62 XX were protein bound. Plasma UH-AC 62 XX levels in rats (n=3/sex) at 6 and 30 hr post a single oral administration of 0.5 mg/kg [^{14}C]UH-AC 62 XX are shown in the following table.

Time (hr)	Mean UH-AC 62 XX Conc. (µg/ml) ♂	♀
6	2.57	1.43
30	1.40	2.32

3.4.1.3. U93-0340 In-vivo plasma protein binding of UH-AC 62 XX (Meloxicam) in humans. (Vol. 2.028, p 260)

Not Reviewed.

3.5. PHARMACOKINETICS OF THE UH-AC 62 XX METABOLITES

3.5.1.1. U92-0314 Blood concentrations and biliary excretion of two main metabolites, AF-UH 1 SE and UH-AC 110 SE, of UH-AC 62 XX in the rat. (Vol. 2.052, p 179)

Study Nº: B85
Report Nº: U92-0314
Study Aims: To determine the PK of two main metabolites of UH-AC 62 XX, AF-UH 1 SE and UH-AC 110 SE, in blood and bile of rats receiving 1 mg/kg of [^{14}C]AF-UH 1 SE or [^{14}C]UH AC 110 SE.
Compound:
Dose and Route:
Animals: ♂ albino rats, (SPF), weighing 226-260 g, 4-7/group.
Study Date: 11/1988 - 10/1989
Blood Sampling: iv, 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 24, 32, 48, 72, and 96 hr post-dose; po, 0, 0.5, 1, 2, 3, 5, 8, 24, 48, and 72 hr post dose.
Bile Collection: 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, and 6 hr post dose

Results: The mean (±SD) PK parameters for AF-UH 1 SE and UH-AC 110 SE following a single dose of 1 mg/kg iv and oral administration to rats are presented in the following table.

Parameters	[^{14}C]AF-UH 1 SE		[^{14}C]UH-AC 110 SE	
	iv	po	iv	po
C_{max} (ng eq/ml)	2567 ± 116	461 ± 200	2700 ± 821	24.3 ± 5.9
T_{max} (hr)	0.08 ± 0.00	0.61 ± 0.11	0.03 ± 0.02	0.70 ± 0.04
$AUC_{0-\infty}$ (ng eq•hr/ml)	2300 ± 274	1308 ± 260	776 ± 77	113 ± 36
MRT_{iv} (hr)	21.6 ± 3.3	21.6 ± 3.3	13.2 ± 5.5	13.2 ± 5.5
MRT_{po} (hr)		27.2 ± 2.7		20.0 ± 8.6
$T_{\frac{1}{2}}$ (hr)	56.5 ± 6.6	56.5 ± 6.6	34.7 ± 10.2	34.7 ± 10.2
$AUC_{partial}$ (%)	25.5 ± 3.3	25.5 ± 3.3	25.5 ± 6.3	25.5 ± 6.3
Clp (ml/min•kg)	7.3 ± 0.9	13.1 ± 2.5	21.7 ± 1.9	159.4 ± 48.6
V_{ss}	9.5 ± 1.7	16.7 ± 2.3	17.3 ± 8.1	117.3 ± 30.8
f_{abs} (%)		56.8 ± 7.7		14.4 ± 3.6

Approximately 2.6% of cumulative (0-6 hr) radioactive dose was recovered in the bile post id administration of 1 mg/kg of UH-AC 110 SE. Contrarily, mean cumulative (0-6 hr) biliary excretion was 33.0% ( ) of radioactive dose post iv administration.

4. LABELING REVIEW

Carcinogenesis, mutagenesis, impairment of fertility

No carcinogenic effect of meloxicam was observed in rats given oral doses up to 0.8 mg/kg (approximately 0.4 the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) for 104 weeks or in mice given oral doses up to 8.0 mg/kg (approximately 2.2 the human dose for 99 weeks.

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow.

Meloxicam did not impair male and female fertility in rats at oral doses up to 9 and 5 mg/kg/day, respectively (4.9 and 2.5 the human dose

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 60 mg/kg (64.5 the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) and embryolethality at oral doses ≥5 mg/kg (5.4 the human dose) when rabbits were treated organogenesis. Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg (approximately 2.2 the human dose organogenesis.

An increased incidence of stillbirths was observed when rats were given oral doses ≥1 mg/kg organogenesis.

Meloxicam crosses the placental barrier [redacted].

Nonteratogenic Effects:

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[redacted]

Labor and delivery

~~In rat studies with meloxicam, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of stillbirths [81], delayed parturition [81,82] and decreased pup survival [82] occurred at daily doses as low as 0.125 mg/kg [82]. This dose is 12 times below the maximum recommended human daily dose of meloxicam on a mg/m^2 basis.~~

[redacted]

Nursing mothers

Studies of meloxicam excretion in human milk have not been conducted; however, meloxicam was [redacted] excreted in the milk of lactating rats [redacted] concentrations higher than those in plasma. Because of the potential for serious adverse reactions in nursing infants from MOBIC®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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5. SUMMARY AND EVALUATION:

5.1. PHARMACOLOGY --

5.1.1. *MECHANISM-RELATED PHARMACOLOGY*

A series of *in vitro* and *in vivo* studies were employed to investigate the possible mechanisms of action mediated by UH-AC 62 XX and results are shown in the following table.

Experimental Model	Route	Parameters Measured	Results
Effects on the Synthesis of PGs			
Zymosan Peritonitis in Mice (PGE_2)	Oral	PGE_2-content of peritoneal exudate	ID_{50} = 1.36 mg/kg
Carrageenin-Induced Pleurisy in Rats (PGE_2)	Oral	PGE_2-content of the pleural exudate	ID_{50} = 0.65mg/kg
Rat - Cotton Pellet Assay	Oral	PGE_2 in exudate 5 hr post single dose	ID_{50} = 0.88 mg/kg
Rat - Cotton Pellet Assay	Topical	PGE_2 in exudate 8 hr post-dose	ID_{50} = 0.94 mg/kg
Rabbit Platelet Poor Plasma - PAF Antagonism	*In vitro*	Effect on PAF-induced platelet agglutination	No inhibition at dose of, $1x10^{-4}$ to $1x10^{-4}$M
Human Synovial Tissue Explants	*In vitro*	Inhibition of prostaglandin biosynthesis	Inhibited at ≥ 0.05 μM
Effects on Cartilage, Macrophages or PMNs			
Human Chondrocytes Explants	*In vitro*	prostaglandin biosynthesis	≥0.5 μg/ml: ↓
Human Articular Chondrocytes			≤5 μg/ml: ↔
Human or Porcine Articular Cartilage	*In vitro*	Synthesis or degradation of proteoglycans	≤100 μM: ↔
Human Synovial Tissue		PGE_2 and IL-1 production	≥0.05 μM: ↓ PGE_2 production by >50% ≤4 μM: ↔ on IL-1 production
PMA or Group A Streptococci Stimulated Human PMNs		Respiratory burst	0.5 μg/ml: ↓ >50%.
TNF, fMLP and PMA Stimulated Human PMNs		Intracellular oxyradical formation	↓ at 50 μM
LPS Stimulated Murine Macrophage Cells (J774)	*In vitro*	Inducible nitric oxide synthase (NOS)	≤ 10 μg/ml: ↔
LPS Stimulated Mouse Macrophage (RAW-264-7) cell line	*In vitro*	Inducible nitric oxide synthase (NOS)	$1x10^{-6}$ to $1x10^{-5}$M: ↔
Human Umbilical Vein Endothelial Cells	*In vitro*	Constitutive NOS	≤ 3×10^{-5}M: ↔
Cultured THP-1 cells	*In vitro*	IL-1β and IL-8 production	≤ 30 μM: ↔
***In Vitro* Differential Inhibition of COX-1 and COX-2**			
Cyclooxygenase from Bull Seminal Vesicles and Bovine Brain	*In vitro*	Inhibition of PG biosynthesis	Bull Seminal Vesicles: EC_{50} = $5.5x10^{-6}$M Bovine Brain: EC_{50} = $1.8x10^{-6}$M
Guinea Pig Cultivated Peritoneal Macrophages	*In vitro*	LPS-stimulated PGE generation	During induction: IC_{50} = 1.91×10^{-9} mg/ml Post Induction: IC_{50} = 4.47×10^{-8} mg/ml Ratio = 23.0
Sheep Placenta Cyclooxygenase	*In vitro*	Inhibition of COX-2	IC_{50} = 6.03×10^{-6}M
Bovine Aortic Endothelial Cells (COX-1) and LPS Stimulated Murine Macrophages (COX-2)	*In vitro*	Inhibition of intracellular COX-1 and COX-2	IC_{50} μg/ml - COX-1, 0.075 μg/ml; COX-2, 0.06 μg/ml. COX-2/-1 Ratio = 0.8
hCOX-1 and hCOX-2 in Transfected COS A.2 Cells, Insect Cells And African Green Monkey Kidney Cells	*In vitro*	Inhibition of intracellular recombinant hCOX-1 & hCOX-2	Whole Cell Assay: IC_{50} (μmol/l) - COX-1, 2.24; COX-2, 0.16
			Microsomal Assay: IC_{50} (μmol/l) - COX-1, 36.6; COX-2, 0.49
Human Whole Blood Assay	*In vitro*	Relative selectivity for inhibition of COX-1 and COX-2	IC_{50} (μg/ml) - COX-1, 3.27; COX-2, 0.25 COX-2/-1 Ratio = 0.8

5.1.2. *PHARMACODYNAMIC EFFECTS RELATING TO PROPOSED INDICATION*

UH-AC 62 XX was demonstrated to have following properties:

- Anti-inflammatory Activity - UH-AC 62 XX was effective in the following animal models.
  - Kaolin-induced hind paw edema model with an ED_{35} value of 7.0 mg/kg;

- carrageenan-induced rat paw edema model with an ED_{35} value of 4.2 mg/kg;
- adjuvant induced arthritis in rats by the inhibition of cartilage destruction, bone lysis, bone proliferation, soft tissues edema and synovial iflammation with an ED_{50} value of 0.28-0.3 mg/kg.

However, it was not effective in the ovalbumin-induced paw edema rat model at an oral dose of up to 16 mg/kg.

- Analgesic Activity - UH-AC 62 XX was shown no to have central analgesic effects in the thermally (hot plate test) and mechanically (tail-clamp test) induced animal pain models. But it was shown to have peripheral analgesic effects in rats using the Randall Selitto assay with an ED_{50} value of 7.72 mg at 45 min and 6.71 at 90 min post single oral dose, respectively.
- Anti-pyretic Activity -
  - UH-AC 62 XX was shown to reduce yeast-induced fever in rats with an ED (-1°C) value of 9 mg/kg.
  - UH-AC 62 XX at an oral dose of 16 mg/kg had no effects on body temperature in normothermic rats.
- Uricosuric Effects -
  - By measurement of the effect on uric acid excretion after treatment rats with oxonic acid, UH-AC 62 XX was shown to be more potent than pheylbuthazone in increasing uric acid excretion with an ED_{50} of 5.6 mg/kg.

5.1.3. SAFETY PHARMACOLOGY

A summary of safety pharmacology study reports is presented in the following table.

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Species/ Model	Route	Type of Study	Findings
Neuropharmacological Effects			
Mouse	Oral (SD)	Sensory function and reflexes	≤ 25 mg/kg: ↔
		Locomotor activity	≤50 mg/kg: ↔
		Barbiturate sleeping time	≤100 mg/kg: ↔
		Muscle relaxation	≤32 mg/kg: ↔
		Pentetrazol-induced and Electric shock	≤50 mg/kg: ↔
		Anticonvulsant effect of phenobarbitone in maximal electroshock	12.5 mg/kg: No interaction
Cardiovascular Effects			
Rat - Conscious Normotensive	Oral (SD)	Systolic blood pressure : 20, 40, and 80 mg/kg	≥20 mg/kg: a slight ↑ in SBP that was not statistically significant
Cat - Anesthetized	IV (SD)	Mean arterial pressure, heart rate, and respiratory min. vol.	≥ 0.1 mg/kg: Statistically significant effect on MABP, HR, and Resp. Min. Vol
Cat - Anesthetized	IV Infusion (SD)	Blood pressure, blood flow, heart rate, respiratory minute volume, and ECG	cumulative dose of 4.0 mg/kg: ↔
Cat - Anesthetized	ID (SD)	MAP, heart rate, and respiratory minute volume: 50, 100, 200 mg/kg	↔
Dog- Conscious Normotensive	Oral (SD)	Mean arterial pressure: 2, 4, and 8 mg/kg	≥2 mg/kg: Slight but not statistically significant ↑
Dog - Anesthetized	IV (SD)	MAP, heart rate, and respiratory minute vol.	1.0 mg/kg: ↑ respiratory minute volume
Rabbit Aorta	*In vitro*	Noradrenaline-induced and spontaneous vesocontractions	≤ 3.0×10^{-6} mol/l: ↔
Guinea Pig - Heart	*In vitro*	Influence on coronary flow, left ventricular pressure, heart rate, and cardiac contractility	1×10^{-5} M: minor effects
Gastrointestinal Effects			
Rat - Stomach Ulcers	Oral (SD)	Measurement of the ulcerogenic activity: 10, 25, 50 mg/kg	UD_{50} = 15.8 mg/kg
Rat - Stomach Ulcers	Oral (SD)	Measurement of the ulcerogenic activity: 1.25, 2.5, 5.0, 10.0, 20.0 mg/kg	UD_{50} = 5.92 (3.65-10.77) mg/kg
Rat	Oral	Incidence of gastric ulcers following administration once daily for 3-day	UD_{50} = 2.31 mg/kg
Rat - GI Erosions and Adjuvant Arthritis	Oral	Determined safety ratio using GI erosion ED_{50} and adjuvant arthritis ID_{50}	Safety Ratio = 20
Rat - Anesthetized	ID (SD)	Gastric acid secretion	ED_{50} = 13.9 mg/kg
Rat - Pylorus Ligated	ID (SD)	Gastric acid and PGE_2 content of gastric secretion	ID_{50} for PGE2 - 8.99 mg/kg ED_{50} for Gastric Acid - 3.43 mg/kg
Rat - Force-Fed	Oral (SD)	Gastric emptying	ED_{50} = >32.0 mg/kg
Rat - Charcoal-Fed	Oral (SD)	Gastrointestinal transit	≤ 32 mg/kg: ↔
Genito-Urinary Effects			
Rat - H_2O and Electrolyte Loaded	Oral	H_2O, Na^+, K^+ and creatinine excretion following administration of a single dose	≤ 8 mg/kg: ↔
Rat - H_2O Loaded	Oral	Excretion of PGE_2 in urine and pleural exudate	ID_{50} (mg/kg) - Urine PGE_2, 1.85; Pleural PGE_2, 0.65.
Bronchial/Pulmonary Effects			
Guinea Pig	IV & ID (SD)	Bradykinin-Induced Bronchospasm - Bronchodilator effect	ED_{50} (mg/kg): ID, 1.13; IV, 0.028
Guinea Pig	IV (SD)	PAF-Induced Bronchospasm - Bronchodilator effect	ID_{50} = 148 μg/kg
Autonomic Nervous System and Smooth Muscle Effects			
Uterus of rat in estrus	*In vitro*	Serotonin and bradykinin induced Contractions	≤1.0×10^{-5} g/ml: ↔
Guinea Pig Ileum	*In vitro*	carbachol-, histamine-, $BaCl_2$-, PGE_2-, and angiotension II, induced contractions	≤1.0×10^{-5} g/ml: ↔
		LTD_4-induced contractions	≤1×10^{-4} M: ↔
Effects on Platelet and Coagulation			
Rabbit Platelets	*In vitro*	Effect on PAF-induced platelet agglutination	1×10^{-6} to 1×10^{-4} M: ↔
Rat	Oral	Measurement of PT: 1, 2, 4, and 8 mg/kg qd x 2-day	↔
Rat	Oral	Measurement of PT : 1, 2, 4, and 8 mg/kg po qd x 2-day + 0.2 mg/kg phenprocoumon	≥4 mg/kg: significantly ↑ the response to phenprocoumon

5.2. TOXICOLOGY

5.2.1. *ACUTE TOXICITY*

Single-dose acute toxicity of UH-AC 62 XX and it's metabolite as well as decomposed UH-AC 62 XX (4.65% decomposition) were accessed in the mouse, rat, and pig. Results are listed in the following table.

Species	Dose (mg/kg)/Route	Length of Observation	Observations
Acute toxicity of UH-AC 62 XX			
Mice	po - 400, 505, 632 ip - 281, 336, 400, 475	2-Week	No information submitted. LD_{50}/ALD_{50}: po - 470 mg/kg; ip - 391 mg/kg
Rats	po - 50, 70.7, 100, 141.4 ip - 39.5, 44.5, 50, 56	2-Week	No information submitted. LD_{50}/ALD_{50}: po - 83.5 mg/kg; ip - 48.0 mg/kg
Rabbits	po - 300, 355, 420	2-Week	No information submitted. LD_{50}/ALD_{50}: 320 mg/kg
Rats SD	po - 50, 70.7, 100, 141.4, 200 iv - 0, 20, 30, 45, 67, 100	2-Week	Oral: 8 deaths (♂: 1 @ 200 mg/kg on Day 5; ♀: 3 @ 100 on Days 6 and 8, and 4 @ 141.4 mg/kg on Days 5, 7, 9, and 11), signs of anemia, reddish nasal discharge, black feces, and emaciated in ♂ @ ≥70.7 and ♀ @ ≥50 mg/kg; iv: 9 deaths (♂: 2 @ 100 mg/kg on Days 4 & 7; ♀: 1 @ 30 on Day 3, 4 @ 45 on Days 3, 4, & 6, and 2 @ 67 mg/kg on Days 6 & 7), signs of ↓ motor activity, black feces, reddish nasal discharge, diarrhea, and anemia in ♂ @ ≥30 and ♀ @ 20 mg/kg. Body weight losses from Days 2 - 7. GI perforations with peritonitis and hemascites or nodules in the pyloric stomach, ileum walls. LD_{50}/ALD_{50}: po - ♂, >200 mg/kg; ♀, 98.4 mg/kg; iv - ♂, >100 mg/kg; ♀, 51.7 mg/kg.
Rats	125, 160, 200 iv	2-Week	200 mg/kg: all died within 6 hr ≥125 mg/kg: deaths (♀ only), lethargic and slow thoracic respiration with marked inspiratory lateral movement of lower ribs; body weight loss; perforated gastric ulcers with peritonitis. LD_{50}/ALD_{50}: ♂, 160-200 mg/kg; ♀, 125-160 mg/kg.
Mini-pigs	50, 100, 200, 400, 800, 1600, 3200 po, dose-escalation	2-Week	≥100 mg/kg: vomiting, diarrhea, ↓ food consumption, lethargy ≥800 mg/kg: Pyloric ulcer/perforation and erosions
Mini-pigs	800, 1600, 3200 po	2-Week	Deaths (≥1600 mg/kg), vomiting, ↓ food consumption, lethargy, gastric ulcer (3200 mg/kg)
Micro-pigs	0, 50, 100, 200 iv	2-Week	Deaths in 200 mg/kg occurred within 3 hr with signs of slight ataxia, dyspnea, lateral positioning and somnolence; vomiting (100 mg/kg). Pathology - blood congestion of the liver and kidneys and subendocardial extravasates in the left ventricle
Acute Toxicity of decomposed UH-AC 62 XX - 4.65% decomposition			
Rats	125, 160, 200 iv	2-Week	Deaths (♂: 200; ♀: ≥125 mg/kg); animals @ 200 mg/kg showed lethargic and thoracic respiration with marked inspiratory lateral movement of the lower ribs, and cyanosis immediately after dosing and expired ~3 hr after dosing; signs of lethargy and lay prone or on the side with chromodacryorrhea noted immediately after dosing in animals @ 125 and 160 mg/kg; chromodacryorrhea, ruffled fur and anemic noted from Day 2 and onwards in animals @ 125 and 160 mg/kg. Pathology - Abnormal gastric mucosa with reddish black stomach contents, blood tinged small intestinal contents, and peritonitis with duodenal perforation (1♀) observed in animals that died during the study; no any pathological changes in all of the surviving animals.
Acute Toxicity of UH-AC 62 XX Metabolites - UH-AC 110 SE, AF-UH 1XX, DS-AC 2 NA, and BIBO 8032 NA			
Rats	UH-AC 110 SE - 50 iv AF-UH 1XX - 70 iv DS-AC 2 NA - 400 iv	2-Week	UH-AC 110 SE and AF-UH 1XX: No toxic effects. DS-AC 2 NA: tachycardia immediately after administration and crouching position, abdominal position and decreased motor activities from 5→60 min after injection.
Rats	BIBO 8032 NA : 294 iv infusion (1.2 ml/min)	2-Week	No toxic effects observed.

5.2.2. *REPEATED-DOSE*

The repeated-dose toxicity of UH-AC 62 XX was evaluated in mice, rats, dogs, and pigs. Findings from each study are summarized as followings.

Species Nº of Animal	Dose/ Route (mg/kg)	Duration	Findings	NOAEL (mg/kg)
Mouse Study				
(SPF) mice 10/sex	0, 8, 17.5, 35 in diet admix	13-wk	Deaths (2♂+1♀ @ 35.0 mg/kg) with macroscopic findings of dark-red discolored lungs and reddened dilated small intestine; ↓ mean body weights in ♂ @ 17.5 and 35mg/kg during Weeks 1-13. Microscopic lesions of perforated ulcer (1♂), chronic ulcer (1♂), and erosion (1♂ + 2♀) in the stomach with or without peritonitis in 35 mg/kg/day; focal ulcerative cholitis (colitis ?) in the large intestine of 1♀ @ 17.5 mg/kg; marked bilateral interstitial fibrosis with mild tubular dilation in the kidney of 1♀ @ 35 mg/kg.	17.5
Dog Studies				
dogs 1/sex/group	0.4, 0.6, 1.2 po	3-wk	One death (♀ @ 1.2 mg/kg) with signs of repeated vomiting and apathetic, ♂ @ 1.2 mg/kg sacrificed on Day 8; ↓ body weights (measured at the time of necropsy) and ↓ food consumption in 1.2 mg/kg (♂+♀) and 0.6 mg/kg (♀). (+) occult stool test in all dogs; gross and microscopic lesions of gastric ulcer in 0.6 and 1.2 mg/kg.	0.4
Beagle dogs 3/sex/group	0, 0.1, 0.2, 0.4 po	4-wk	No toxic effects. **MTD was not achieved.**	>0.4
Pig Studies				
micropigs 3-6/sex/group	0, 1, 3, 9 iv	4-wk plus a 6-week recovery phase	No toxic effects. **MTD was not achieved.**	>9
minipigs 3/sex/group	0, 1, 3, 9 iv	5-wk plus a 6-week recovery phase	Gross lesions of ulcers (~1 cm diameter, 2♀ @ 9 mg/kg), purulent bronchopneumonia (1♀ @ 9 mg/kg), and abscess in the injection site (1♂ @ 1.0 and 1♂ and 1♀ @ 9.0 mg/kg); microscopic lesions of ulcers in 2♀ and healed ulcers in one recovery ♀ @ 9 mg/kg.	3
minipigs 3-6/sex/group	0, 1, 3.5, 10 po	13-wk plus a 6-wk recovery phase	Gross and microscopic lesions of gastric ulcers in 1♀ @ 3.5 mg/kg and 1♂ @ 10 mg/kg; histopathological lesions of purulent bronchopneumonia in 1♂ and 1♀ @ 3.5 mg/kg.	1
minipigs 4/sex/group	0, 1.0, 3.0, 9.0 po	52-wk	5 unscheduled deaths (2♀ @ 1.0 mg/kg; 1♀ @ 3.0 mg/kg; 2♂ @ 9.0 mg/kg) with signs of lethargy, listless, hypothermia, ataxia, and loss of appetite prior to death; and ↓ food consumption with lower body weight. Gross lesions of gastric ulcer (~4 cm in diameter) in 1♀ @ 9.0 mg/kg and acute→chronic bronchopneumonia in 2 @ 0, 6 @ 1, 5 @ 3, and 3 @ 9 mg/kg. Microscopic lesions of chronic gastric healed ulceration/scarring in 1♀ @ 9 mg/kg & 1♂ @ 3 mg/kg, respectively.	3
minipigs 6/sex/group	0, 1, 2.5, 6 po	52-week plus a 13-week recovery phase	No toxic effects. **MTD was not achieved.**	>6

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Species Nº of Animal	Dose/ Route (mg/kg)	Duration	Findings	NOAEL (mg/kg)
Rat Studies				
Rat 5/sex	0, 2, 5, 10, 20, 30, 40, 50 po	4-wk	Deaths (1♀ @ 10, 2♂+5♀ @ 20, 5♂+5♀ @ 30, 40, & 50 mg/kg); GI ulcers/perforations with peritonitis were major pathological lesions observed in all dead and 3 surviving (2 @ 10 mg/kg and 1 @ 20 mg/kg) rats	♂: 10 ♀: 5
[redacted] (SPF) rats 10-20/sex/group	0, 0.2, 0.4, 0.8, 1.6 iv	4-wk with a 8-wk recovery	Slightly ↑ NAG excretion value (↑27%) during Week 4 but not Week 12 in ♂ @1.6 mg/kg; (+) occult blood tests in 2♂ @ 1.6 mg/kg during Week 4; no gross pathological lesions; microscopic changes in the stomach - erosions (2♂ @ 0.4 & 3♂ + 2♀ @ 1.6 mg/kg) and ulcer (4♂ + 1♀ @ 1.6 mg/kg) and kidney - pyelonephritis (1♀@ 0 & 4♂ @ 1.6 mg/kg).	0.8
[redacted] (SPF) rats 5/sex/group	0, 1.0, 2.0, 4.0, 6.0, 8.0 iv	4-wk	Rats @ 8 mg/kg were sacrificed during Week 1 due to poor general health condition; 1 death (♂ @ 6 mg/kg); signs of anemic, lethargic, loss of appetite, reduced H_2O uptake, and deep breathing in the rats @ ≥4 mg/kg/day; ↓ in RBC, Hb, and Ht, ↑MCV, ↑reticulocytes, ↑WBC with ↑ PMN; ↓ in ALP, LAP, choline esterase, albumin, and total protein in ≥4 mg/kg; ↑ epithelial excretion in ♂ & ♀ @ 6 mg/kg; ↑ NAG excretion in ♀ @ 4 and 6 mg/kg, and ↑ protein excretion in ♀ @ 6 mg/kg; GI-erosions and ulcers/perforations in the stomach, ileum, and/or cecum; kidneys-pyelonephritis and papillary necrosis.	♂: 1 ♀: <1
[redacted] (SPF) rats 12-24/sex/group	0, 1.0, 3.5, 10.0 po	13 wk with 6-week recovery phase	30 deaths (1♂ @ 3.5 mg/kg - gavage error; 11♂ & 18♀ @ 10 mg/kg - perforated GI ulcers with peritonitis); signs of dark feces, tender abdominal walls, and pale appearance with significant ↑ (♂: ↑~35%; ♀: ↑74%) in H_2O intake in animals @ 10 mg/kg; ↑WBC, PMN, and lymphocyte, ↓RBC, Ht, Hb, and MCHC with ↑MCV, ↑reticulocyte, ↓platelet, ↓total protein with ↓albumin and A/G ratios in 10 mg/kg; ↑PMN in ♀ @ 3.5 mg/g; peptic pyloric ulcers in 3.5 mg/kg (9/12♂ and 11/12♀); pyloric and/or duodenal perforation with peritonitis (11/12♂ and 12/12♀; recovery animals: 9/12♂ and 8/12♀), swelling in epithelial cells of proximal renal tubule sections with brownish lysosomal residual bodies (6/12♂ and 5/10♀; 1 recovery ♀) and pyelonephritis/pyelitis (1♂ and 1 recovery ♂) in 10 mg/kg.	1.0
Sprague-Dawley (Jcl) rats 15-25/sex/group	0, 1, 2.5, 7 po	3-mon plus a 6-week recovery phase	Deaths (7♀ @ 7 mg/kg) due to GI toxicity with clinical signs of anemia, black feces, emaciation and hypothermia; ↑WBC, PMN, monocyte and lymphocyte, ↓RBC, Ht, and Hb (♀ only), ↑reticulocyte, ↑platelet, and ↓total protein with ↓albumin in 7 mg/kg; (+) occult fecal blood in 1♀ @ 2.5 and 1♂ + 7♀ @ 7 mg/kg; ↑ relative and absolute kidney and spleen weight in all UH-AC 62 XX treated groups; blood-tinted or yellowish green ascites, adhesions of abdominal organs, intestinal ulcers in all 7dead ♀; gross lesions of ulcerous scar in the stomach (one each ♂ @ 1 and 2.5 mg/kg, 1♀ @ 7 mg/kg) plus cecum (1♂ @ 7 mg/kg) and erosion in the stomach (1♂ @ 7 mg/kg); microscopic ulcers in stomach (1♂), jejunum (1♀), ileum(1♀), and cecum (3♂ + 1♀) in 7 mg/kg, papillary edema in 1♂ + 2♀ @ 2.5 and 4♂ + 2♀ + 1 recovery ♀ @ 7 mg/kg, pyelonephritis/chronic purulent nephritis (murine nephritis caused by bacterial infection) in 1♀ @ 1 mg/kg, 3♂ + 1♀ + 1 recovery ♀ @ 7 mg/kg ,and papillary necrosis, in 2♀ + 1 recovery ♀ @ 7 mg/kg.	1.0
Wistar rats 20/sex/group	0, 0.2, 0.4, 0.8 po	12-mon	No toxic effects were observed; therefore, **MTD was not achieved.**	>0.8
[redacted] (SPF) rats 24/sex/group	0, 1.0, 2.0, 3.5 po	18-mon	A dose dependent increase in the mortality rate (3♂+1♀ @ 1.0, 2♂ + 4♀ @ 2.0, and 6♂ + 14♀ @ 3.5 mg/kg); signs of anemic, wet bedding, intense urine odor, and blood-tinged urine in 3.5 mg/kg; ↑H_2O intake (2.0 & 3.5 mg/kg); ↓ mean body weight in all UH-AC 62 XX treated groups. ↑WBC, PMN, monocyte and lymphocyte; ↓RBC, Ht, and Hb, and ↑reticulocyte; ↑platelet; ↓total protein with ↓albumin; ↓total cholesterol; ↓total glycerol in 2.0 & 3.5 mg/kg; ↑ incidence of blood-tinted urine in UH-AC 62 XX treated ♀; GI ulcers/erosion and papillary necrosis with or without pyelonephritis in all UH-AC 62 XX treated groups.	<1.0

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Species Nº of Animal	Dose/ Route (mg/kg)	Duration	Findings	NOAEL (mg/kg)
Dog Studies				
[redacted] dogs 1/sex/group	0.4, 0.6, 1.2 po	3-wk	One death (♀ @ 1.2 mg/kg) with signs of repeated vomiting and apathetic, ♂ @ 1.2 mg/kg sacrificed on Day 8; ↓ body weights (measured at the time of necropsy) and ↓ food consumption in 1.2 mg/kg (♂+♀) and 0.6 mg/kg (♀). (+) occult stool test in all dogs; gross and microscopic lesions of gastric ulcer in 0.6 and 1.2 mg/kg.	0.4
Beagle dogs 3/sex/group	0, 0.1, 0.2, 0.4 po	4-wk	No toxic effects. **MTD was not achieved.**	>0.4
Pig Studies				
[redacted] micropigs 3-6/sex/group	0, 1, 3, 9 iv	4-wk plus a 6-week recovery phase	No toxic effects. **MTD was not achieved.**	>9
[redacted] minipigs 3/sex/group	0, 1, 3, 9 iv	5-wk plus a 6-week recovery phase	Gross lesions of ulcers (~1 cm diameter, 2♀ @ 9 mg/kg), purulent bronchopneumonia (1♀ @ 9 mg/kg), and abscess in the injection site (1♂ @ 1.0 and 1♂ and 1♀ @ 9.0 mg/kg); microscopic lesions of ulcers in 2♀ and healed ulcers in one recovery ♀ @ 9 mg/kg.	3
[redacted] minipigs 3-6/sex/group	0, 1, 3.5, 10 po	13-wk plus a 6-wk recovery phase	Gross and microscopic lesions of gastric ulcers in 1♀ @ 3.5 mg/kg and 1♂ @ 10 mg/kg; histopathological lesions of purulent bronchopneumonia in 1♂ and 1♀ @ 3.5 mg/kg.	1
[redacted] minipigs 4/sex/group	0, 1.0, 3.0, 9.0 po	52-wk	5 unscheduled deaths (2♀ @ 1.0 mg/kg; 1♀ @ 3.0 mg/kg; 2♂ @ 9.0 mg/kg) with signs of lethargy, listless, hypothermia, ataxia, and loss of appetite prior to death; and ↓ food consumption with lower body weight. Gross lesions of gastric ulcer (~4 cm in diameter) in 1♀ @ 9.0 mg/kg and acute→chronic bronchopneumonia in 2 @ 0.6 @ 1.5 @ 3, and 3 @ 9 mg/kg. Microscopic lesions of chronic gastric healed ulceration/scarring in 1♀ @ 9 mg/kg & 1♂ @ 3 mg/kg, respectively.	3
[redacted] minipigs 6/sex/group	0, 1, 2.5, 6 po	52-week plus a 13-week recovery phase	No toxic effects. **MTD was not achieved.**	>6

5.2.3 *CARCINOGENICITY*

The carcinogenic potentials of SC-58635 were accessed in rats and mice.

- Rat Study - Groups of Crl:CD BR Sprague-Dawley rats were given UH-AC 62 XX in the diet at doses of 0, 0.4, 0.6, and 0.8 mg/kg for 104 weeks. There were no effects on mortality, clinical signs, food consumption, body weight/body weight gain, hematology, ophthalmology, auditory acuity, and dentition. No treatment-related gross pathological changes were identified. Significant non-neoplastic microscopic findings were limited to the kidney, papillary necrosis (2♂ + 12♀ @ 0.6 mg/kg; 1♂ + 23 ♀ @ 0.8 mg/kg) and pyelonephritis (8♀ @ 0.8 mg/kg). However, no significant GI lesions were characterized. Papillary necrosis and pyelonephritis are often recognized as toxic effects caused by long term treatment with NSAID; thus, the MTD was achieved for both ♂ and ♀.
  Comparable incidence of all examined tumors was noted in both controls and UH-AC 62 XX treated groups. Thus, UH-AC 62 XX, up to 0.8 mg/kg, was not carcinogenic in rats following 104-week repeated doing via diet admix.

- Mouse Study - Groups of [redacted](SPF)[redacted]mice were given UH-AC 62 XX in the diet at doses of 0, 2, 4, and 8 mg/kg for 99(♀)/104(♂) weeks. There were no effects on mortality, clinical signs, food consumption, body weight/body weight gain, hematology, ophthalmology, auditory acuity and dentition. No treatment-related non-neoplastic gross and microscopic pathological lesions were identified. Therefore, the MTD was not achieved in the current study. However, data presented in a 13-week dose ranging study showed GI lesions was observed in mice @ 17.5 (1♀, focal ulcerative colitis) and 35 mg/kg (1♂, perforated ulcer; 1♂, chronic ulcer; and 1♂ + 2♀, erosion with or without peritonitis) groups. "Colitis" was observed in only 1♀ @ 17.5 mg/kg;

therefore, it might not be treatment-related. NOAEL for mice in the 13-week range finding study was 17.5 mg/kg. Apparently, MTD lies between 17.5 and 8 mg/kg.

Significant positive trend for hepatocellular adenoma and pituitary adenoma was noted by the sponsor in ♀ with p values of 0.0049 and 0.023, respectively using Peto's analysis method (time-adjusted). However, the analysis performed by the agency's statistician showed that p values for hepatocellular adenoma and pituitary adenoma were 0.0148 and 0.4450, respectively using the exact permutation trend test. A significant p value of 0.039 was noted for hepatocellular adenoma + carcinoma by the [redacted] But, it was not shown to be significant with the [redacted] time-adjust test as stated by the sponsor. A p value of 0.033 for hepatocellular adenoma + carcinoma was obtained by the agency's statistician using the exact permutation trend test.

Both hepatocellular adenoma and pituitary adenoma are common tumors based on concurrent controls or historical data provided by the sponsor; therefore, these statistical values might not implicate any biological significance. Therefore, UH-AC 62 XX was not carcinogenic in mice following repeated oral dosing via dietary feeding for ≥99 weeks at doses up to 8.0 mg/kg.

5.2.4. *REPRODUCTIVE TOXICOLOGY*

The following table summarizes the effects of UH-AC 62 XX on fertility, reproductive functions, embryo-fetal development, and peri-/post-natal development.

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Animals Species	Dose (mg/kg)	Duration of Treatment	Observations
FERTILITY, EARLY EMBRYONIC DEVELOPMENT→IMPLANTATION (SEG. I)			
♂ & ♀ Rats	♂: 0, 1, 2.5, 9; ♀: 0, 1, 2.5, 5	♂: 9-week prior to mating → the end of study ♀: 2-week prior to mating→GD 7	Signs of anemic in 1 ♂ @ 9 mg/kg and dark brown feces in 2♀ @ 5 mg/kg; ↓ mean body weight in ♀ @ 2.5 and 5.0 mg/kg during GD 15-21. Fertility - no effects on estrous cycle, fertility and copulation indexes. Female Reproductive and Litter Parameters - ↓ Nº of corpora lutea in ♀ @ 5 mg/kg; at doses ≥2.5 mg/kg, ↑ early resorption and ↓ implantation rates, ↓ implantation sites (≥1 mg/kg), and ↓ Nº of live fetuses; ↓ Nº of ossification centers of cervical vertebral body at all dose groups and ↓ Nº of ossification centers of sacral and coccygeal vertebrae at 5 mg/kg. NOAEL: parental toxicity, ♂: <1 mg/kg, ♀: 1 mg/kg; fertility, ♂: 9 mg/kg, ♀: 5mg/kg; ♀ reproductive toxicity, 2.5 mg/kg; fetal developmental toxicity, <1 mg/kg; not teratogenic up to 5 mg/kg.
TERATOLOGY- EMBRYO-FETAL DEVELOPMENT (SEG. II/III)			
♀ Rats (SPF)	0, 1, 2, 4	GD 7→16	Effects on the F_0 Dams: 6 deaths (1 @ 2 and 5 @ 4 mg/kg) and 4 of theses 6 with GI ulcers during necropsy; ↑ gestation in dams @ 2 and 4 mg/kg; ↓ Nº of implantations and viable fetuses in dams @ 1 mg/kg. Effects on the F_1 Pups: ↓ PND 7 survival rate (90.9% vs 94.1%) in pups @ 1 mg/kg; ↓ mean body weights (↓5-11%) accompany with ↓ body weight gains (↓12-14%) in pups @ 1 mg/kg during PND 7→21; delayed development of hair covering and opening of auditory canals in 2-3 pups @ 1 mg/kg group. NOAEL: maternal toxicity, 1 mg/kg; reproductive toxicity, 1 mg/kg, embryo/fetal toxicity, 4 mg/kg. Not teratogenic up to 4 mg/kg.
♀ Rats	0, 1, 2, 4	GD 7→17	Effects on the F_0 Dams: Pathology - Gastric ulcers in 4, 7 and 10 @ 1, 2, and 4 mg/kg, respectively at GD 21 sacrifice and 1 @ 4 mg/kg at delivery (PND 0). Reproductive Performance and Litter Parameters - ↑ length of gestation in dams @ ≥1 mg/kg; ↑ Nº of stillbirths in 4 mg/kg. Effects on the F_1 Pups: ↓ 4-day survivals in pups born to dams @ 4 mg/kg. NOAEL: maternal toxicity, <1 mg/kg; reproductive toxicity, <1 mg/kg; embryo/fetal and developmental toxicity, 2 mg/kg. Not teratogenic up to 4 mg/kg.
♀ Rabbits (SPF)	0, 5, 20, 80	GD 6→18	7 deaths (1 @ 0 and 6 @ 80 mg/kg) due to either dosing errors (1 each @ 0 and 80 mg/kg) or drug-related GI injury; body weight losses during Gestation Days 6-9 and ↓body weight gains in dams @ 80 mg/kg; dose-dependent ↓ in the Nº of implantations and viable fetuses. ↑ in pre-implantation loss and resorption rates. NOAEL: maternal toxicity, 20 mg/kg; embryo/fetal toxicity <5 mg/kg; not teratogenic up to 80 mg/kg.
♀ Rabbits (SPF)	0, 1, 20, 60	GD 6→18	5 deaths in 60 mg/kg with pathological findings of hemorrhages in gastric or intestinal mucosa and/or ulcers in the GI; dose-dependent ↑ in resorption rate and total Nº of resorptions. Malformations: 60 mg/kg, septal defect of heart in 2/43 and one of these with marked dilation of the aorta arch and the other one with cleft lip, cleft palate, unilateral anophthalmia, and facial bones shortened and laterally disarranged; 20 mg/kg, no gall bladder in 1/97; 1 mg/kg, fused sternebrae in 2/92. NOAEL: maternal toxicity, 20 mg/kg; embryo/fetal toxicity 1 mg/kg.
♀ Rabbits (SPF)	0, 1, 3, 8, 20	GD 6→18	Slightly ↑ incidence in total (early + late) Nº of resorptions in 20 mg/kg. **Fetal examinations were not performed.** NOAEL: maternal toxicity, 20 mg/kg; embryo/fetal toxicity 8 mg/kg.
PERINATAL/POST NATAL DEVELOPMENT (SEG. III)			
♀ Rats	0, 0.125, 0.25, 0.5	GD17→LD 21	Effects on the F_0 Dams: 5 deaths with signs of piloerection, anemia, and dark feces; a slight ↓ in mean body weight (↓5-6%) in 0.5 mg/kg dams during LD 0→7; gastric ulcers in 4/4 ♀ @ 0.5 mg/kg that died during gestation period; 3/6 @ 0.25 mg/kg and 7/12 @ 0.5 mg/kg that had no livebirths or lost all pups during lactation; 1 each dam @ 0.25 and 0.5 mg/kg/day at PND 21. Reproductive Performance - dose-dependently ↑ gestation period and the length of delivering time, ↓birth index, ↑Nº of stillbirths and ↓ Nº of live births. Effects on the F_1: Dose-dependent ↑ in F_1 pups mortality during PND 0→4; ↓ Nº of implantations in F_1 dams at 0.5 mg/kg. Effects on the F_2 fetuses: no external abnormalities. NOAEL: maternal toxicity, 0.125 mg/kg; reproductive toxicity of F_0 and F_1, <0.125 and 0.25 mg/kg, respectively; developmental toxicity, <0.125 mg/kg. Not teratogenic up to 0.5 mg/kg.

5.2.5. *GENETIC TOXICOLOGY*

The mutagenic potentials of UH-AC 62 XX were evaluated in both *in vitro* and *in vivo* systems and results are summarized in the following table.

Assay System	Indicator Cells	UH-AC 62 XX Conc.	Findings
		1, 10, 25, 100, 250, 500, 1000, 2500, and 5000 μg/plate	Precipitation occurred at concentrations ≥2500 μg/plate. **The positive control, benzoapyrene was not working properly; therefore, the study was invalid.**
		20, 100, 500, 1000, 2500 μg/plate	Not mutagenic at doses up to 2500 μg/plate in the absence and presence of S9 activation.
		200 and 400 mg/10 ml/kg po single dose for TA 97 and TA 100; 150 and 300 mg/kg po for TA 98	**"Equivocal " as the positive controls, cyclophosphamide and 2-AF did work properly.**
		62.5, 125, 250, 500 μg/ml	No increased incidence of mutant cells under current testing condition was observed; **however, it is difficult to make a conclusion stating that UH-AC 62 XX was not mutagenic as cells only exposed briefly to meloxicam (2 hr).**
		-S9: 5, 25, 50, and 250 μg/ml; +S9: 10, 50, 100, 500, 1000, 2000 μg/ml	Not clastogenic to human lymphocyte at doses up to 50 μg/ml.
		300 mg/10 ml/kg po single dose	A slight increased mean % MNE/1000 PE was noted for UH-AC 62 XX treated ♂ at 24 hr post dose with a value of 0.28% vs 0.1% in the controls.
		75, 150, and 300 mg/10 ml/kg po single dose	Not clastogenic.

5.2.6. *SPECIAL TOXICOLOGY*

The antigenic properties and the potential to cause skin sensitivity of UH-AC 62 XX was evaluated and the observations are summarized in the following table.

Testing System	Species	UH-AC 62 XX (Dose/Route)	Observations/Comments
Guinea Pig Maximization Test	Chbb:DPH Guinea Pigs	Sensitization: 2.5 mg in 0.1 ml FCA*/vehicle id[b] Induction and Challenge: 2.5 mg in 0.1 ml vehicle	Not immunogenic.
Guinea Pig Maximization Test	Pirbright Albino Guinea Pigs	Sensitization: 0.1 ml 0.3% eye drops in FCA/vehicle id[b] Induction and Challenge: 2 ml 3% eye drops	**No concurrent + control was performed. Therefore, the study was not valid.**
Guinea Pig Maximization Test	Pirbright Albino Guinea Pigs	Sensitization: 0.1 ml 1% cream in FCA/vehicle id[b] Induction and Challenge: 2 ml 1% cream	**No concurrent + control was performed. Therefore, the study was not valid.**
Guinea Pig Maximization Test	Chbb:DPH Guinea Pigs	Sensitization: 0.1 ml 1% gel in FCA/vehicle id[b] Induction and Challenge: 2 ml 1% gel	Not immunogenic.
Popliteal Lymph Node Assay	♀ BALB/c mice	1 mg/0.02 ml and 2 mg/0.04 ml intra-footpad injection	**"Equivocal " as the positive controls, did work properly in 2/4 experiments.**

* FCA = Freund's Complete Adjuvant; [b] id = intradermal injection.

5.2.7. *TOXICITY RELATED TO THE STARTING MATERIAL, 2,5-AMTH*

The following table shows the summary of toxicological findings for the starting material (2,5-AMTH; 2-Amino-5-Methylthiazole) in various studies. This compound was also identified as one of degradation products in the final drug product.

Testing System	Species/Indicator	2,5-AMTH Dose/Route	Findings
Acute Single-Dose Toxicity	♂ & ♀ Wistar Rats	500, 1000mg/10ml/kg po	LD_{50}: ♂, ~812.5; ♀, ~687.5. 10 deaths (1♀ @ 500; 4♂+5♀ @ 1000 mg/kg) occurred within 24 hr post dosing with clinical signs of ↓ activity, ↑ pain reactions, ↓ body and abdominal tone, ↓ ear and plantary reflex, ↓ respiratory rate, ↓ reaction to noise, piloerection, ↑ salivation, ↑lacrimation, and abdominal or sqatting position occurred within 10 min post-dose. Gross lesions of redness of the renal pelvis and medulla, redness of the glandular stomach or the gastric mucosa.
Acute Single-Dose Toxicity	♂ & ♀ Rats	2000 mg dermal application	↓ body temperature and signs of sedation, prone position and piloerection observed within 7 hr after local application of AMTH; these observations subsided by 24 hr after removal of plaster containing AMTH; body weight losses in ♂ during Days 2→4 and ♀ during Days 2→7. No gross lesions identified.
Repeated-Dose Toxicity	♂ & ♀ Rats	0, 4, 20, 100 mg/10 ml/kg po	Signs of sedation and rough coat; ↓ mean body weights with ↓ cumulative weight gains and food consumption in the 100 mg/kg; reduction in food intake during Week 1/2 in 20 mg/kg. ↓WBC, ↓lymphocyte, ↑platelet, ↑TPT, ↑ cholesterol and CHE (♂ only) in 100 mg/kg; ↑ absolute thyroid weight. ≥20mg/kg: thymic atrophy, follicular cell hypertrophy in thyroid; 100 mg/kg: pituitary gland - depiction of acidophils and hyperplasia of basophils; thyroid - follicular cell hyperplasia; liver - hepatocellular hypertrophy; spleen - red pulp depletion (♂ only); lung - foam cell accumulation; atrophy of adrenal cortex (♂ only).
Primary Dermal Irritation	♂ & ♀ Rabbits	263.2 mg/plaster/site x3 dermal application	Not a skin irritant
Primary Eye Irritation	♂ & ♀ Rabbits	20 mg topical ocular application	**An ocular irritant** - moderate to severe redness of conjunctiva with swelling of the lids observed in all treated eyes at 1, 6, and 24 hr post dose but not 72 hr
Dermal Sensitivity (Guinea Pig Maximization Test)	Guinea Pigs	Sensitization: 1% in Na-CMC or FCA/H_2O id Induction and Challenge: 50% in Vaseline, dermal topical	Not a dermal sensitizer.
Salmonella/microsomal Ames Assay		100, 500, 1000, 2500, 5000 μg/plate	**Mutagenic:** 1000 μg/plate: slight dose-dependent increases (↑10-84%) in the mutation rates in the tester strains TA 100 and TA 102 with or without activation S9
Chromosome Aberration		-S9: 50, 250, 500, 750, 1000 μg/ml; +S9: 250, 750, 1500 μg/ml	**Clastogenic:** -S9: 1000 μg/ml +S9: 1500 μg/ml
Micronucleus Assay	♂ Rats	20, 100, and 500 mg/kg po single dose	**Equivocal:** 500 mg/kg - significantly ↓ PE ratios at 24 (↓51%) and 48 hr (↓54%) post dose, an indicative of myelotoxicity; slight but dose-dependent ↑ in the incidence of MNE
Unscheduled and Replicative DNA Synthesis	♂ Rats	20, 100, and 500 mg/kg po single dose	**No increase in the incidence of** unscheduled or replicative (S-phase) DNA synthesis in primary rat hepatocytes

5.3. ADME

5.3.1. ABSORPTION AND PHARMACOKINETIC/TOXICOKINETICS

5.3.1.1. Single-Dose plasma PK Parameters for UH-AC 62 XX in the Mouse, Rat, Dog, Pig, and Baboon

- Mouse Study -10 mg/kg iv and po

PK Parameters	Oral			IV
	♂ + ♀	♂	♀	♂ + ♀
C_{max} (µg eq/ml)	18.14	16.7	19.35	36.63
T_{max} (hr)	0.7	0.6	0.6	
$AUC_{0-\infty}$ (µg eq•hr/ml)	60.74	44.36	69.65	64.69
$MRT_{0-\infty}$ (hr)	3.89	2.72	3.55	3.02
$T_{1/2}$ (hr)	4.76	1.8	2.39	6.41
V_{ss} (l/kg)				0.47
Clp (ml/min•kg)	2.74			2.58
F (AUC_{oral}/AUC_{iv})	0.94			

- Rat Study - 1 mg/kg iv and po

Parameters	♂		♀	
	po	iv	po	iv
C_{max} (µg eq/ml)	2.35	-	3.23	
T_{max} (hr)	4.4	-	6.8	
$AUC_{0-\infty}$ (µg eq•hr/ml)	83.3	70.9	201.0	217.0
$MRT_{0-\infty}$ (hr)	31.8	18.0	53.4	52.6
$T_{1/2}$ (hr)	49.9	13.4	52.4	36.8
Clp (l/hr•kg)	0.023	0.015	0.01	0.005
V_{ss} (l/kg)	0.257	-	0.244	-

- Food Effect on PK Parameters in Rat - 1 mg/kg iv and po
  Slightly increased AUC and C_{max} values were noted in non-fasted rats. In addition, food also slightly delayed UH-AC 62 XX absorption as higher T_{max} value was noted in non-fasted animals.

Parameters	Fasted (♂)		Non-fasted (♂)
	iv (n=4)	po (n=5)	po (n=5)
C_{max} (µg eq/ml)		3.23 ± 0.73	3.95 ± 0.47
T_{max} (hr)		6.4 ± 1.7	7.6 ± 2.6
$T_{1/2}$ (hr)	15.5 ± 5.3	14.5 ± 3.1	12.3 ± 3.8
$AUC_{0-\infty}$ (µg eq•hr/ml)	121.5 ± 65.3	83.3 ± 27.7	102.0 ± 41.4
MRT (hr)	14.9 ± 6.0	17.8 ± 3.9	16.7 ± 5.0
CL_{tot} (ml/min•kg)	0.17 ± 0.09		

- Dog Study - 7.5 mg/kg po; 15 mg/kg iv and sc

Parameters	Oral		Intravenous		Subcutaneous	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
C_{max} (µg/ml)	0.464	12.7	-	-	0.734	15.9
T_{max} (hr)	7.5	110	-	-	2.5	74.8
$AUC_{0-\infty}$ (µg•hr/ml)	22.9	16.0	21.5	13.1	24.1	16.3
$MRT_{0-\infty}$ (hr)	40.0	21.9	34.8	23.6	35.0	13.1
$T_{1/2}$ (hr)	23.7	30.0	24.0	26.5	23.7	18.0
Clp (l/hr•kg)	0.009	14.7	0.01	13.0	0.008	17.1

- ♂ Mini-Pig Study - 1 mg/kg po, n=3

Parameters	UH-AC 62 XX Formulations		
	ZB 334	ZB 335	TK 736A
$T_{1/2}$ (hr)	8.0	8.33	5.0
$AUC_{0-\infty}$ (µg•hr/ml)	6.961	7.175	5.006
$MRT_{0-\infty}$ (hr)	10.71	12.84	6.65
C_{max} (µg/ml)	0.696	0.728	0.82

- ♂ Baboon Study - 10 mg/kg po, n=3

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Parameters	Mean	CV (%)
C_{max} (μg eq/ml)	34.15	29.6
T_{max} (hr)	6.0	33.3
$AUC_{0-\infty}$ (μg eq•hr/ml)	475.6	26.7
MRT_{iv} (hr)	11.2	18.7
$T_{½}$ (hr)	6.12	13.7
Clp (ml/min•kg)	0.022	31.3

5.3.1.2. Repeated Oral Dose Study in Rats

PK parameters	Dose (mg/kg)					
	1.0 x 5-day		1.0 x 11-day		0.3 x 11-day	
	♂	♀	♂	♀	♂	♀
C_{max} (μg eq/ml)	1.38	1.49	6.4	7.5	1.48	2.44
T_{max} (hr)	0.5	1	4.2	13.1	5.2	8.31
AUC (μg eq•hr/ml)	12.34	18.78	172	437	38.8	153
MRT_{iv} (hr)			24.0	48.6	20.7	55.8
$T_{½}$ (hr)			15.5	29.6	12.6	36.7

5.3.1.3. Pharmacokinetics of UH-AC 62 XX metabolites, AF-UH 1 SE and UH-AC 110 SE - 0.1 mg/kg iv and po

Parameters	[^{14}C]AF-UH 1 SE		[^{14}C]UH-AC 110 SE	
	iv	po	iv	po
C_{max} (ng eq/ml)	2567 ± 116	461 ± 200	2700 ± 821	24.3 ± 5.9
T_{max} (hr)	0.08 ± 0.00	0.61 ± 0.11	0.03 ± 0.02	0.70 ± 0.04
$AUC_{0-\infty}$ (ng eq•hr/ml)	2300 ± 274	1308 ± 260	776 ± 77	113 ± 20
MRT_{disp} (hr)	21.6 ± 3.3	21.6 ± 3.3	13.2 ± 5.5	13.2 ± 5.5
MRT_{iv} (hr)		27.2 ± 2.7		20.0 ± 3.6
$T_{½}$ (hr)	56.5 ± 6.6	56.5 ± 6.6	34.7 ± 10.2	34.7 ± 10.2
$AUC_{partial}$ (%)	25.5 ± 3.3	25.5 ± 3.3	25.5 ± 6.3	25.5 ± 6.3
Clp (ml/min•kg)	7.3 ± 0.9	13.1 ± 2.6	21.7 ± 1.9	159.4 ± 48.6
V_{ss}	9.5 ± 1.7	16.7 ± 2.3	17.3 ± 8.1	117.3 ± 30.8
$f_{rel\,AUC}$ (%)		56.8 ± 7.7		14.4 ± 3.6

5.3.1.4. Toxicokinetics

- Mouse: cacinogenicity study

Week	Mean (±SD) Plasma UH-AC 62 XX Levels (μg/ml)	
	Dose - 4 mg/kg/day	
	♂ (N=20)	♀ (N=20)
1	0.157 ± 0.062[a]	0.146 ± 0.047[b]
30	0.542 ± 0.165	0.378 ± 0.169
60	0.561 ± 0.130	0.509 ± 0.174
80	0.450 ± 0.198	0.564 ± 0.319

[a] N=17; [b] N=6.

- Rat: 1-year oral toxicity study

Compound	Dose (mg/kg)	Plasma Drug Levels (μg/ml)							
		Week 1		Week 7		Week 13		Week 52	
		♂	♀	♂	♀	♂	♀	♂	♀
UH-AC 62 XX	0.2	0.71	2.7	0.78	3.0	1.1	3.0	1.2	3.7
	0.4	1.1	4.2	1.6	4.5	1.7	4.2	2.4	7.7
	0.8	2.3	6.6	3.0	8.5	4.4	9.8	3.5	12
Piroxicam	0.8	0.57	3.7	0.97	4.7	0.63	3.6	0.76	5.6

- Pig: 52-week repeated oral toxicity study

Dose (mg/kg/day)	C_{max} (μg/ml)			AUC_{0-24} (μg•hr/ml)		
	Day 1	Week 25	Week 52	Day 1	Week 25	Week 52
1.0	0.480	0.722	0.518	5.065	7.878	6.710
2.5	1.398	1.040	0.868	13.015	12.232	12.982
6.0	3.165	3.220	2.092	35.818	42.792	30.150

5.3.2. *TISSUE DISTRIBUTION*

5.3.2.1. Rat

UH-AC 62 XX was well distributed into the majority of tissues as demonstrated by a rat tissue distribution study. Following a single oral or iv dose of 1 mg/kg [^{14}C]UH-AC 62 XX, the blood contained the highest concentrations of radioactivity at 1 or 5 and 9 hr post doing, with high levels of radioactivity also found in well perfused tissue/organs, such as lungs, heart, liver, and kidneys. The concentrations of radioactivity in pigmented and non-pigmented skin were similar and decreased at similar rates, indicating that there was no preferential binding of UH-AC 62 XX to melanin. By 96 hours post dose, concentrations of radioactivity in most tissues were below the limit of detection. Data from repeated oral or iv dose study showed that the liver and kidney had highest concentrations of radioactivity. Blood and thyroid gland also showed significant amounts of exposure. Lower levels were seen in the lungs, trachea, heart, skin, pancreas, and salivary glands. The brain and eyes had very low but detectable amounts of radioactivity. T_{max} value for most tissues was 4 hr except the liver and kidney that had peak levels of radioactivity 8 hr after dosing. Similar tissue distribution patterns were noted for female rats; however, markedly higher levels of radioactivity were detected in the ♀, indicating that ♀ had a slower elimination rate than ♂.
Data from the whole-body autoradiography study with [^{14}C]UH-AC 62 XX (1 and 10 mg/kg iv and 5 mg/kg po) showed that the liver had highest radioactivity. Relative high radioactivity was detected in the blood, lungs, skin and kidneys. A lower concentration was detected in the skeletal muscles and only slight traces of radioactivity were shown in the central nervous system. In addition, [^{14}C]UH-AC 62 XX and its metabolites have no affinity for pigmented layers in the skin or eyes.

5.3.2.2. Pig

Tissue distribution of radioactivity in ♂ and ♀ pigs were performed by given a single oral dose of [^{14}C]UH-AC 62 XX, 3.5 mg/kg. The highest concentrations of radioactivity were identified in the intestines, kidneys, liver and bile at 4 hr post-dose.

5.3.3. *METABOLISM*

5.3.3.1. Mouse

Metabolic Profile in Plasma - About 83-87% of radioactivity present in the plasma was as parent compound and ~6-7% of radioactivity was derived from AF-UH 1 (5'-hydroxymethyl metabolite).
Metabolic Profile in Urine - The major metabolites identified in the urine were 5'-hydroxymethyl metabolite (AF-UH 1) (51%), 5'-carboxyl metabolite (UH-AC 110) (4.5%), and thiourea derivative (UH-AC 101) (2.8%).

5.3.3.2. Rat

Metabolic Profile in Urine - The major metabolites identified in the albino rat urine were acid metabolite (UH-AC110; 15.6%), alcohol metabolite (UH-AF1; 31.4%), and DS-AC 2 SE, a metabolite with the cleavage of side chain, (21.7%). Similar metabolic profiles were identified in black-hooded rats.

Treatment of rats with UH-AC 62 XX, 15 mg/kg po for 3 days did not alter the relative liver weight, protein and P-450 content, and metabolic enzyme activities (EROD, PROD, and ECOD)

5.3.3.3. Pig

Metabolic Profile in Plasma, Urine, and Feces - The major radioactivity (~60-80%) detected in the plasma was derived from unchanged drug following a single oral and iv dosing of 10 mg/kg [^{14}C]UH-AC 62 XX. The unchanged drug represented ~1% and 17% in the urine and feces, respectively after both oral and iv administrations. Two major metabolites, M1 and M2, were detected in the urine and feces. M1 might be a conjugate of M2. About 50% and 5-6% of radioactivity in the feces derived from M2 and M1, respectively. In contrast, M1 and M2 comprised ~34 and 13% of radioactivity, respectively in the urine.

5.3.4. EXCRETION

5.3.4.1. Mouse

Urinary and Fecal Excretion - The elimination of radioactivity was primarily through urinary (67%) and fecal (35%) excretions following a single oral dose of 10 mg/kg [^{14}C]UH-AC 62 XX. Approximately 50% of total radioactivity dose were detected in the urine by 8 hr post dose

5.3.4.2. Rat

Urinary and Fecal Excretion - Approximately, 92.2% and 69.3% of total radioactivity eliminated by 96 hr post a single iv dose of 1 mg/kg [^{14}C]UH-AC 62 XX were noted in ♂ and ♀, respectively. Urine was the major excretion route. No gender differences in the patterns of excretion via urine and feces. The eliminated total radioactive dose in the urine was 2-3x higher than that in the feces. Apparent gender difference in renal excretion was noted as ♂ had higher cumulative excretion of radioactive dose in the urine. In addition, ♀ had slower elimination rate as only 69% dose was eliminated at 72 hr post oral dosing while ♂ had 91% of total dose was eliminated during the same time period.
Biliary Excretion - Biliary excretion of radioactivity was nearly completed in ♂ by 48 hr post iv administration of 1 mg/kg [^{14}C]UH-AC 62 XX. Mean cumulative biliary excretion of total radioactive dose was 19.8% in ♂ and 12.5% in ♀. Approximately 11% of radioactivity was excreted in the bile of ♂ rats following intra-duodenal injection of the pooled bile collected from donor rats that had received an iv dose of 1 mg/kg [^{14}C]UH-AC 62 XX.

5.3.4.3. Pig

Excretion in Urine and Feces - The total radioactivity recovered 120 hr post a single oral or iv dosing of 10 mg/kg [^{14}C]UH-AC 62 XX was ~86%. Cumulative total radioactivity (0-120 hr) eliminated through the feces (po, 45.8; iv, 43.6%) was lightly higher than that in the urine (po, 33.5%; iv, 38.9%).
Similar results were obtained from 13-week repeated oral toxicity study. Approximately 94% and 100% of total radioactive dose was eliminated following a single and 13-week repeated doing with 3.5 mg/kg UH-AC 62 XX. Cumulative total radioactivity (0-120 hr) eliminated via urine and feces was 45.3% and 48.4%, respectively for single dose and 51.7% and 49.3%, respectively for 13-week repeated dose.

5.3.5. PROTEIN BINDING

- Mouse - Approximately 97% of the drug were protein bound over the range of 0.5-20.0 μg/ml of [^{14}C]UH-AC 62 XX *in vitro*.

- Rat - More than 99% of UH-AC 62 XX were protein bound post a single oral administration of 0.5 mg/kg [^{14}C]UH-AC 62 XX, and the binding between plasma protein and UH-AC 62 XX could not be displaced by the addition of 78.5 μg acid metabolite, UH-AC 110XX. Results from *in vitro* experiments showed that binding of UH-AC 62 XX to rat plasma proteins was 98-99% at concentrations of 0.24-20.33 μg/ml.
- Mini-pigs - Approximately 95.5% of [^{14}C]UH-AC 62 XX were protein bound following a single oral dose of 3.5 mg/kg.
- Human - *In vitro* protein binding studies showed that ~ 99% of UH-AC 62 XX bound to plasma protein at concentrations of 0.5-50 μg/ml.

5.3.6. *PLACENTAL TRANSFER AND MILK SECRETION*

Secretion of UH-AC 62 XX through milk was evaluated in the lactating rats [redacted] by given a single oral dose of 5 mg [^{14}C]UH-AC 62 XX via gavage. The levels (μg eq/ml) of total radioactivity dose was higher in the milk than in the blood or plasma at 5 and 24 hr post, implying that [^{14}C]UH-AC 62 XX was excreted into milk extensively and available to neonates.

Placental transfer of UH-AC 62 XX was assessed by giving a single oral dose of 1 mg/kg [^{14}C]UH-AC 62 XX to pregnant rats at GD 13 (n=6) and 18 (n=12). Results from quantitation of radioactivity in tissues/organs showed that higher levels of radioactivity in the fetus and amniotic fluid in rats dosed on GD 18 than those dosed on GD 13. The levels of radioactivity in the maternal corresponding tissues/organs were higher than in the fetus. In addition, high levels of radioactivity were detected in tissues of newborn pups on postnatal Day 6. Furthermore, whole body autoradiographs of pregnant (GD 19) rats showed that distribution of radioactivity in the fetal skeletal muscle was higher than in the maternal muscle. Therefore, based upon these observations, UH-AC 62 XX crossed the placenta and was available to the fetus.

6. CONCLUSIONS AND RECOMMENDATIONS:

Meloxicam (MOBIC™), an enolic acid (oxicam) group of nonsteroidal anti-inflammatory drug (NSAID), was shown to have anti-inflammatory and peripheral analgesic properties. Meloxicam has been developed for the treatment of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and other rheumatic indications. Various formulations of meloxicam (tablets, capsules, suppositories, and ampoules) have been marketed in over 70 countries outside of the US for the treatment of inflammatory diseases. In the current petition, the proposed indication is to treat signs and symptoms of OA.

Preclinical toxicology studies showed that GI and kidney were major target organs for UH-AC 62 XX induced toxicity following repeated oral administration to the rat and pigs. It also shown to have embryo/fetal lethality when given to pregnant rats during early embryo development, organogenesis or late gestation period. It was also shown to delay parturition, increase the length of delivery time, and reduce neonatal survival in rats. Similar toxicity profiles have been seen in animals treated with other NSAIDs. Results from a rabbit embryo-fetal development study (Study Nº 82-0509) showed septal defect of heart observed in 2/43 fetuses (4.7%) at 60 mg/kg. Although data from another embryo-fetal development study (Study Nº U82-0078) showed no malformations observed in fetuses from dams @ 80 mg/kg, it is difficult to obtain the consistency between these two studies as low number of litters and fetuses were evaluated. However, the incidence of cardiovascular defect in the rabbit is rare (provided historical control: 0.01%); therefore, the relationship of observed malformation to treatment with UH-AC 62 XX in the Study Nº 82-0509 cannot be excluded and should be stated in the labeling.

3 *pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.*

/S/ 11/29/99

W.C. Josie Yang, Ph.D.

Concur by team leader: Yes ☒ No ☐

/S/ 11-29-99

Andrea Weir, Ph.D.

cc:
NDA 20-938
HFD-550/Division File
/JYang
/AWeir
/KJohnson
/AZeccola
HFD-345
F/T by JYang, November 22, 1999

8. APPENDIX

8.1. EXECUTIVE CAC RECOMMENDATIONS AND CONCLUSIONS ON CARCINOGENICITY STUDIES

Executive CAC
September 7, 1999

Committee: Jim Farrelly, Ph.D., HFD-530, Acting Chair
Joseph Contrera, Ph.D., HFD-900, Member
Al DeFelice,, Ph.D., HFD-110 Alternate Member
Andrea Weir, Ph.D., HFD-550, Division Team Leader
Josie Yang, Ph.D., HFD-550, Presenting Reviewer

Author of Draft: Josie W. C. Yang
The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA N°: 20-938
Name of Drug: Mobic® (Meloxicam)
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Background
Meloxicam (UH-AC 62 XX, $C_{14}H_{13}N_3O_4S_2$) is a nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid (oxicam) class. Meloxicam has been developed for the treatment of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and other rheumatic indications. Various formulations of meloxicam (tablets, capsules, suppositories, and ampoules) have been marketed in over 70 countries outside of the US for the treatment of inflammatory diseases. Meloxicam was shown not to be mutagenic in an Ames assay nor clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow. Both rat and mouse carcinogenicity study protocols had not been previously presented to the Executive CAC.

Rat Carcinogenicity Study
Groups of Crl:CD BR Sprague-Dawley rats were given UH-AC 62 XX in the diet at doses of 0, 0.4, 0.6, and 0.8 mg/kg for 104 weeks. There were no effects on mortality, clinical signs, food consumption, body weight/body weight gain, hematology, ophthalmology, auditory acuity, and dentition. No treatment-related gross pathological changes were identified. Significant non-neoplastic microscopic findings were limited to the kidney, papillary necrosis (2♂ + 12♀ @ 0.6 mg/kg; 1♂ + 23 ♀ @ 0.8 mg/kg) and pyelonephritis (8♀ @ 0.8 mg/kg). However, no significant GI lesions were characterized. Papillary necrosis and pyelonephritis are often recognized as toxic effects caused by long term treatment with NSAIDs; thus, MTD was achieved for both ♂ and ♀.
Comparable incidence of all examined tumors was noted in both controls and UH-AC 62 XX treated groups. Thus, UH-AC 62 XX, up to 0.8 mg/kg, was not carcinogenic in rats following 104-week repeated dosing via diet admix.

Mouse Carcinogenicity Study
Groups of HAN Bö (SPF) NMRI mice were given UH-AC 62 XX in the diet at doses of 0, 2, 4, and 8 mg/kg for 99(♀)/104(♂) weeks. There were no effects on mortality, clinical signs, food consumption, body weight/body weight gain, hematology, ophthalmology, auditory acuity and dentition. No treatment-related non-neoplastic gross and microscopic pathological lesions were identified. Therefore, MTD was not achieved in the current study. Data from a 13-week dose ranging study showed GI toxicity was observed in mice @ 17.5 (1♀ with gross findings of adhesions of ileum and colon in the region of appendix and microscopic lesions of focal ulcerative colitis) and 35 mg/kg (perforated ulcer in 1♂; chronic ulcer in 1♂; and erosion in 1♂ + 2♀). Clearly, MTD lies between 17.5 and 8 mg/kg.

Significant positive trend for hepatocellular adenoma and pituitary adenoma was noted by the sponsor in ♀ with p values of 0.0049 and 0.023, respectively using Peto's analysis method (time-adjusted). However, the analysis performed by the agency's statistician showed that p values for hepatocellular adenoma and pituitary adenoma were 0.0148 and 0.4450, respectively using the exact permutation trend test. A significant p value of 0.039 was noted for hepatocellular adenoma + carcinoma by the [redacted] But, it was not shown to be significant with the Peto's time-adjust test as stated by the sponsor. A p value of 0.033 for hepatocellular adenoma + carcinoma was obtained by the agency's statistician using the exact permutation trend test.

Both hepatocellular adenoma and pituitary adenoma are common tumors based on concurrent controls or historical data provided by the sponsor; therefore, these statistical values might not implicate any biological significance.

Executive CAC Recommendations and Conclusions:

1. The Committee found that rat carcinogenicity study was acceptable. Based on observed pathological findings in the kidney, papillary necrosis and pyelonephritis, MTD was reached.
2. No toxic effects on all monitored parameters (mortality, clinical signs, body weights, hematology, gross and histopathology) were observed; therefore, MTD was not achieved in the mouse study. However, the committee reassessed data from a 13-week dose-ranging study and concluded that the high-dose employed in this 2-year study was sufficiently near to MTD to consider the study adequate for the assessment of carcinogenicity.
3. The committee concluded that both rat and mouse studies were adequate and negative for carcinogenicity.

/S/ 5/15/99

Jim Farrelly, Ph.D.
Acting Chair, Executive CAC

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